

CRITICAL CARE

Emergency Medicine

SECOND EDITION



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CRITICAL CARE EMERGENCY MEDICINE

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“Guérir parfois, soulager souvent, consoler toujours”

—Ambroise Paré

I would like to dedicate this book to my father Dr. Jean Pierre Farcy for his love and for sharing his passion for medicine and life. Dr. Thomas M. Scalea for being a great mentor, teacher, and most of all a friend who is always there when I need guidance. To my Mother, Poeia, Eve, Frederic, and Sarah, for their patience, support, and unconditional love.

—David A. Farcy

To all those who have been influential to me: Terri, Anthony, Katherine, Victoria, and the extended Shock Trauma family.

—William C. Chiu

With much love to my wife, Seriti, and my boys, Sahm, Siahvash, and Kianoosh, whose patience and support make everything possible.

And with deep gratitude to my teachers, the patients, from whom I learned everything I know about medicine.

—John P. Marshall

To my amazing husband Jeff and children Ashley and David Osborn for their unwavering love and support. In loving memory of my mother Edna L. Medlin, who dedicated her life to education. To my father and brothers, W. Lee, Christopher and Mitchell Medlin for your love and encouragement. In appreciation of my mentors and educators, who provided the light of education and the example of ethics.

Most importantly, this book is dedicated to our patients and their families. To trust in our care enough to invite us into the most personal aspects of their lives, during their most vulnerable periods, is the greatest honor and responsibility any person or profession can be bestowed.

—Tiffany M. Osborn

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Critical care by its very nature is a multidisciplinary disease. Virtually every critically ill patient requires input from a multiplicity of practitioners. Physicians in the ICU provide direct care, and orchestrate and coordinate care for all other practitioners who participate. Given this complexity, it is interesting to note that critical care has been a recent development. The first true multidisciplinary ICU was opened in 1958 at the Baltimore City Hospital, now named Johns Hopkins Bayview. It was also the first ICU that had 24-hour physician coverage.

Critical care was rapidly becoming its own discipline, yet it lacked efficient organization. In 1970, 28 physicians met in Los Angeles and formed the Society of Critical Care Medicine. The society's leaders and first three presidents were Peter Safar, an anesthesiologist; William Shoemaker, a surgeon; and Max Harry Weil, an internist. Throughout the 1970s, 1980s, and 1990s, these three disciplines represented the backbone of critical care in the United States.

As critical care began to develop, emergency medicine also began to develop as a real discipline. In 1961, Dr James Mills started a full-time emergency medicine practice in Alexandria, Virginia. The American College of Emergency Physicians was founded shortly after that, in 1968. Residency training began at the University of Cincinnati, followed by the Medical College of Pennsylvania, and then the Los Angeles County Hospital. Finally, in 1979, the American Board of Emergency Medicine was approved. Other institutions then developed emergency medicine residencies. Today, there are over 150 accredited programs. Fellowship training followed in subspecialties such as toxicology, pediatrics, and now critical care.

The link between emergency medicine and critical care seems natural—both require understanding of complex physiology. Practitioners in both specialties must understand a multitude of diseases, synthesize solutions for complex problems, and do this quickly. When I founded the Department of Emergency Medicine at SUNY Downstate and Kings County Hospital in 1991, we created a 4-year residency program that was heavy in critical care. However, I soon realized that emergency physicians who wanted to practice real critical care would need additional training. Thus, when I became the Physician-in-Chief at the R Adams Cowley Shock Trauma

Center, I established a critical care fellowship designed for emergency physicians. The University of Pittsburgh had been training emergency physicians for some time in its multidisciplinary critical care fellowship. There are now over 100 fellowship-trained emergency physician intensivists. Over two-thirds of them are trained at either Shock Trauma or the University of Pittsburgh. Many graduates practice in major academic centers and now provide leadership roles in these institutions.

Emergency physician intensivists have become commonplace in ICUs. This will continue. Emergency physicians who wish to be leaders will need to be clinically excellent, academically productive, and superior educators. The current textbook goes a long way toward establishing emergency physicians as credible intensivists. Although not every chapter is written by an emergency physician, many are. The authors are emergency physicians who most of us expect to become the leaders in critical care. The book is unique, as it blends the perspective of a true intensivist with that of emergency medicine. The book is the first of its kind, and I predict it will become known as the standard reference for those emergency physicians, as well as others, who wish to understand the overlap between emergency medicine and critical care.

Despite the lack of board certification and many other local political impediments, some emergency physicians have embraced critical care clinically, academically, and now in this textbook. The role of emergency physicians in critical care remains controversial, but the controversy is not as sharp as it was at the beginning. Those of us who have been there from the beginning look forward to the day that there will be no controversy left at all.

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PREFACE



With great pleasure and appreciation, we present the second edition of *Critical Care Emergency Medicine*. This book is a dedicated resource for those who diligently provide care for the sickest patients in emergency departments and intensive care units around the world—you. The emergency physician defines the quality interface between emergency medicine and critical care. We are proud and honored to provide a trusted resource to your armamentarium.

This edition provides updated recommendations, addressing the challenges faced by the emergency physician practicing critical care on the front lines of health care every day. Much like our clinical practice, it is written collaboratively by emergency physicians and colleagues from trauma, critical care, infectious diseases and pulmonary medicine. We are fortunate and appreciative to have these national and international

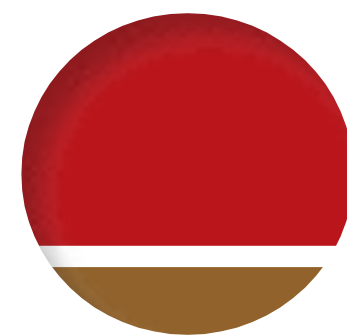
experts contributing to a resource that is now readily available to you anytime of the day or night.

We would like to express our deepest gratitude to Mary Bennett for her diligent review and editorial expertise, Executive Medical Editor Brian Belval, Senior Project Development Editor Regina Brown, Associate Project Manager Dinesh Pokhriyal, and the entire staff at McGraw-Hill for their countless hours of providing us with guidance, direction, and at times, editorial “resuscitation.” A special thanks to former Executive Medical Editor Ann Sydor for her vision and dedication in making the first edition a reality.

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INTRODUCTION



History and Update in Critical Care Certification

Brian T. Wessman • Kyle J. Gunnerson • Emanuel P. Rivers • Debra Perina

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“Critical care medicine... quo vadis?”¹ (translation: where are you going?)

- Peter Safar, MD

“Current politics preventing emergency medicine from getting additional critical care medicine subspecialty certification is wrong.”

- Dr. Peter J. Safar, *Careers in Anesthesiology: An Autobiographical Memoir*, 2000

Critical care is a continuum initiated by prehospital care, continues with emergency medicine (EM) resuscitation and stabilization, and culminates with intensive care unit (ICU) management.^{1,3} Since the formation of the Society of Critical Care Medicine in 1970, a multidisciplinary approach, including EM, has been advocated for the practice of critical care medicine (CCM).⁴ Today, emergency medicine physicians (EMPs) are actively pursuing formal critical care training and certification to join the existing ranks of board-certified intensivists.

EMERGENCY MEDICINE RESIDENCY TRAINING

EM and CCM require proficient acumen in treating life-threatening acute illness. EM focuses on the early hours of disease treatment while CCM is weighted toward more prolonged management within the ICU.⁴ Graduates of EM residency programs are unique in their training and background, making them ideal candidates for CCM training. EM residencies exist as three- (70%) and four-year (30%) training cycles. A unique strength of EM training is that

the Accreditation Council for Graduate Medical Education (ACGME) Residency Review Committee (RRC) requires that the trainee receive broad exposure to the undifferentiated critical care patient (see Figure 1).⁶ With estimates of a 60% increase in Emergency Department (ED) critical care volume and a reported 1.4 million patients admitted to the ICU through the ED, the EMP staff is a primary portal of entry and provides the most proximal, time-sensitive care for the critically ill and injured.²¹ EMPs provide hundreds of patients critical care annually in this country.⁵ EM residency also provides a training curriculum with rotations in the ICU (basic RRC requirement of four months) and in-patient floor settings (both medical/surgical). EM residents become adept at multitasking and providing critical care for emergent cardiac failure (STEMI, heart failure, arrhythmias cardiopulmonary failure, etc.), acute neurologic events (stroke, status epilepticus, intracranial hemorrhage, etc.), respiratory failure (hypoxia, COPD, asthma, PNA, etc.), sepsis, toxicology, blunt/penetrating trauma patient, GI hemorrhage, wound care, burn injuries, metabolic derangements, and so on.⁶

Also expected of the EM graduate is procedural acumen with emergent airway stabilization, vascular/arterial access, thoracostomy, para/thora/cardiocentesis, and point-of-care ultrasound imaging, amongst other procedures (see Figure 2).⁶

EMERGENCY MEDICINE AND CRITICAL CARE MEDICINE HISTORY

EM and CCM share multiple common historical threads, having begun around the same time and sharing overlapping developments. Both specialties are concerned with the acute deterioration of the patient. Additionally, the expanding

ED Undifferentiated Critical Care Patient Populations	
Emergent cardiac arrest: STEMI, heart failure, arrhythmias, cardiopulmonary failure, etc.	Acute neurologic events: stroke, status epilepticus, intracranial hemorrhage, etc.
Respiratory arrest: hypoxia, COPD, status asthmaticus, PNA, etc.	Trauma patients: blunt, penetrating, environmental, burns, traumatic brain injury, etc.
Severe sepsis/Septic shock	Toxicology
GI hemorrhage	Orthopedic emergencies and wound care
Obstetric and Gynecologic emergencies	Metabolic emergencies: DKA, thyroid, adrenal crisis, etc.
Palliative care, EOL	Oncologic emergencies
Understand 24/7 in-house patient care and shift work...	

ACGME Program Requirements for Graduate Medical Education in Emergency Medicine, 2012.
(STEMI: ST-elevation myocardial infarction, COPD: chronic obstructive pulmonary disease, PNA: pneumonia, GI: gastrointestinal, EOL: end-of-life, DKA: diabetic ketoacidosis)

FIGURE 1 Typical Emergency Department (ED) patient population that provides critical care experience for the EM resident.

body of resuscitation research heavily influenced the development of both specialties in the 1960s.⁷ EM and CCM are multidisciplinary endeavors whose breadth and depth of knowledge extends across traditional departmental and specialty lines as both deal with organ system derangements in decompensating patients. The following timeline helps to identify some unique intersecting historical points in the U.S. development of both specialties:

- 1968: American College of Emergency Physicians was formed, focusing on emergency and critical care medicine.
- 1970: Society of Critical Care Medicine was formed with a multidisciplinary approach to critical care medicine with the inclusion of EM.
- 1979: American Board of Emergency Medicine (ABEM) formed and emergency medicine becomes the 23rd medical specialty.
- 1979: CCM becomes a subspecialty sponsored by American Board of Internal Medicine (ABIM),

Procedural Acumen Required During EM Residency	
Emergent airway stabilization	Vascular/arterial access
Thoracostomy	Point-of-care ultrasound imaging
Para/thora/cardio/arthrocentesis	Lumbar puncture
Joint manipulation/splinting	Incision & Drainage
Sedation	Advanced wound care
Cardioversion	BLS/ACLS/ATLS (code patients)

ACGME Program Requirements for Graduate Medical Education in Emergency Medicine, 2012.
(BIS: Basic Life Support, ACLS: Advanced Cardiac Life Support, ATLS: Advanced Trauma Life Support)

FIGURE 2 Typical CCM procedures that an EM resident is expected to master during residency.

American Board of Surgery (ABS), and American Board of Pediatrics (ABP).

- 1986: ABEM applies for co-sponsorship of CCM subspecialty (not approved by ABMS).
- 1989: ABMS approves ABEM as a primary board (removal of conjoint board status).
- 1998: ABEM and ABIM initiate talks to co-sponsor a six-year residency training pathway for triple certification in emergency medicine, internal medicine, and critical care medicine (pathway announced September 1999).
- 2004: White paper on national critical care shortage with potential implications.
- 2004: FOCCUS paper published on framing options for critical care in the United States.
- 2006: White paper published on emergency medicine and critical care medicine certification.
- 2006: Discussion reinitiated between ABEM and ABIM regarding CCM fellowship and certification for EM residency graduates.
- 2011 (September): Institute of Medicine report published a paper on crisis in emergency departments.
- 2011 (September): ABMS approved ABEM and ABIM co-sponsorship of CCM fellowship training pathway leading to the first training and ABMS certification pathway for EM residency graduates.
- 2012 (February): Unilateral sponsorship by ABS for surgical-based critical care fellowship training pathway for EM residency graduates.
- 2013 (July): ABMS approved ABEM and American Board of Anesthesiology (ABA) co-sponsorship of ACCM fellowship training pathway.

Canada and parts of Europe recognized the specialty of emergency medicine, along with IM, surgery, anesthesiology, and pediatrics, as acceptable base training programs for CCM eligibility.⁷

Emergency medicine trainees have been pursuing and completing CCM fellowships through various venues since the late 1970s but no formal pathway to United States certification existed for graduates of EM residencies until the 2011 announcement.⁴ Lacking access to certification in the United States, many EM/CCM trainees sought formal certification from the European Society of Intensive Care Medicine. Currently, there are over 220 EM/CCM fellowship trained physicians practicing in various models in the United States. The majority of these EM/CCM pioneers practice at major academic centers with prominent clinical and academic roles at the local and national/international level.⁸

EM/CCM PATHWAYS TO CERTIFICATION MEDICINE

Since September 1999, the American Board of Internal Medicine (ABIM) and American Board of Emergency Medicine (ABEM) have conjointly sponsored an extended residency pathway that allows for potential CCM certification.⁹ This

combined residency program, entered through a match out of medical school, is six years in duration and at completion, allows the trainee access to sit for triple board certification in EM, internal medicine (IM), and CCM. Critical care didactic curriculum and clinical training is interspersed during the six-year time frame, with a heavier clinical component of CCM over the final two years of training. Close interaction and cooperation is required between a sponsoring institution's primary residencies of EM and IM to provide adequate didactics and clinical experience. Limitations exist for the number of trainees allowed in this pathway due to potential impact on trainees in the core residencies.⁹

Currently, four programs offer combined EM/IM/CCM training pathways:

- University of Maryland Medical Center
- Henry Ford Hospital Program
- Long Island Jewish Medical Center, Albert Einstein College of Medicine
- Vidant Medical Center/East Carolina University of Medicine

In September 2011, ABMS approved a co-sponsored pathway by ABIM and ABEM to CCM fellowship training and certification after successful completion of an EM residency.¹⁰ Specifics of the ABIM/ABEM CCM pathway include a 24-month curriculum and a prerequisite of completing six months of internal medicine exposure, with a required three months specifically in a dedicated medical intensive care unit (MICU) setting, prior to, or in conjunction with, the start of the fellowship training.¹⁰ The CCM fellowship curriculum requires an additional six months of MICU clinical exposure at the Fellow level, but does allow some latitude with multidisciplinary critical care rotations and further ICU time for the remainder of the two-year training cycle. A stipulation stating that only 25% of trainees can be EM/CCM in a medicine critical care fellowship does create a limit of potential available training slots.¹⁰ The IM-Residency Review Committee also has stipulations in place that exclude EM/CCM graduates who pass the ABIM-CCM certifying exam, the ability to supervise medicine residents in training during their MICU rotations.¹¹

The first ACIM-CCM certification exam (through a "practice pathway clause") was offered in 2012. Twenty-five diplomats took this initial certifying exam with all of them successfully obtaining certification.¹² By 2014, a total of 44 EM diplomats have taken the ABIM-CCM certification exam with a 100% pass rate (traditional national first time IM pass rate is 92%).¹³ There are currently thirty-four IM-CCM training programs with variability between programs willing to accept EM residency graduates.

SURGERY

In February 2012, the American Board of Surgery (ABS) announced their intention to create access to surgical critical care (SCC) training for EM residents after successful completion of an EM residency.¹⁴ This pathway resulted from an

agreement with ABEM and received ABMS approval, without direct co-sponsorship. Specifics of the ABS pathway include completion of 24 months of training, broken into two 12-month blocks that must be completed at the same training institution. The first year (12-month block) requires primary exposure as an advanced preliminary resident to surgical rotations (as determined locally by the Surgery Residency Director and the SCC Fellowship Program Director).¹⁵ During this year, some intermediate-level operative time (i.e., thoracic or abdominal operative cases) must be included to provide exposure to complex surgical conditions.¹⁶ No more than 3 months of time in a surgical intensive care unit (SICU) setting are allowed during this first year of training. The second year (12-month block) is completion of the standard SCC training curriculum. SCC programs wishing to have an EM/CCM training program must submit their proposed first year curriculum to the ABS for approval. No "grandfathering pathway" was offered with the announcement of this critical care certification pathway. The first annual available certification exam was offered in 2015.

ANESTHESIOLOGY

In July 2013, ABMS approved a co-sponsored pathway to critical care medicine certification from the American Board of Anesthesiology (ABA) and ABEM.¹⁷ The ABA/ABEM co-sponsored pathway is unique in its approach to be all-inclusive and to create the potential flexible framework for a well-rounded multidisciplinary clinical-based training curriculum for the EM/CCM fellow.¹⁷ The EM applicant has the prerequisite of needing to complete four months (16 weeks) of ICU rotations during residency (standard RRC requirement for all EM residency graduates) as well as successfully completing an ACGME EM residency. The pathway requires that all EM/CCM fellows complete 24 months of training in an approved ACCM curriculum. This is required of EM applicants, regardless of whether they have completed a 3-year (36-month) or 4-year (48-month) residency program. The 2-year curriculum requires that both years of training be completed at the same ACCM site. During the first 6 months of fellowship training, the EM/CCM fellow should have exposure to at least 3 surgical-based rotations and by completion of the 24-month cycle, the EM/CCM fellow should have completed a total of 12 months of surgical exposure.¹⁸ However, latitude does exist in how to define "surgical exposure." For example, this requirement could be met in a "mixed" Medical/Surgical ICU, or rotations such as nephrology and infectious disease as long as sufficient exposure to surgical patients was gained. The requirements also encourage multidisciplinary critical care exposure to rotations such as pulmonary medicine, bronchoscopy, cardiology, neurologic disorders, as well as anesthesiology rotations (pre-op or peri-operative rotations). This pathway is a clinical-based curriculum and requirements do stress that no more than two elective rotations (2 months) can be spent pursuing research.¹⁸

ACCM programs must apply for formal EM/CCM two-year curriculum approval through the ABA.¹⁸ A limited

	Medicine (CCM)	Surgery (SCC)	Anesthesiology (ACCM)
Sponsors	ABIM and ABEM	ABS	ABA and ABEM
Length of Training	24 months	12 months + 12 months	24 months
Focus	Medicine	Surgery	Multidisciplinary
Pre-requisites	–6 months of medicine (3 MICU) –EM residency	None	–4 months of ICU –EM residency
Special training requirements	–6 months of MICU –Only 25% EM/CCM	1 st year of surgical exposure	–Surgical and mixed exposure –Clinical
Certification Exam	ABIM exam	ABS exam	ABA exam

FIGURE 3 Matrix comparing the three approved pathways (Internal Medicine, Surgery, Anesthesiology) for EM residents to obtain formal fellowship training and critical care board certification.

grandfathering/clinical practice pathway will remain in effect until 2018. The first ACCM certification exam including EM/CCM trainees was offered in 2014. Fourteen EM/CCM diplomats were approved to take this exam. Twelve were successful for an initial pass rate of 86% (traditional national first time ACCM pass rate is 85%).¹⁹ Currently, seventeen programs have received approval by the ABA for an EM/CCM two-year training curriculum. An updated list may be found at <http://www.theaba.org/TRAINING-PROGRAMS/Resident-Options/ACCM-Fellowships>.

The three potential pathways leading to formal EM/CCM board certification are a major development for both specialties (see Figure 3). A well-established potential fourth pathway through a two-year fellowship training curriculum in neurocritical care medicine is also available for EM residency graduates but does not currently lead to ABMS board certification.

UNIFIED CURRICULUM AND EM/CCM FUTURE

The need for critical care services is increasing as the gap between supply and demand for intensivists grows.^{3,4} The pipeline of practicing intensivists remains relatively stagnant at about 12,000 U.S. adult CCM-certified physicians.²⁰ This discordance between patient need and physician supply has potential to worsen patient outcomes, threaten patient safety, and increase healthcare costs.³ EM/CCM is a newly recognized member of this community and has the potential to be a part of the solution.

The co-sponsored agreements for EM/CCM formal certification will allow for the growth of multidisciplinary training curriculums and foster growth within the CCM specialty. This has already been seen, as EM trainees have been paramount in bringing point-of-care ultrasound clinical usage into the ICU setting. Unfortunately, the three pathways to certification have created confusion amongst EM residents interested in pursuing critical care training. Further developments for EM/CCM training should focus on developing cohesive training curriculums that focus on the end product

of a well-rounded intensivist. This will only help to unify the specialty of EM/CCM instead of fractionating it into three separate entities. Similar recommendations to harmonize all critical care training across specialties in the United States have been published.²⁰

At one point in the history of U.S. medicine, the emergency department was divided into quadrants of medicine, surgery, OB/GYN and pediatrics. It took the creation of the specialty of emergency medicine to help break down this barrier and unite a hospital-based medical specialty. Perhaps critical care medicine, as a similar hospital-based medical specialty, could learn from this history as it invites the specialty of EM/CCM into the fold.

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AIRWAY AND VENTILATORY SUPPORT

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Approach to the Difficult Airway

Jason C. Wagner

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CASE VIGNETTE

A 40-year-old female presented at 8:00 A.M. with a swollen lip but no rash, speaking full sentences. She was immediately given intravenous diphenhydramine, methylprednisolone, and famotidine. At 10:30 A.M., she developed neck swelling, difficulty swallowing, and dyspnea and was given subcutaneous epinephrine and nebulized albuterol while an anesthesiologist was called for possible difficult airway intubation and an otolaryngologist was called for possible emergent tracheostomy. The patient decompensated and the anesthesiologist was unable to intubate the patient. The otolaryngologist took 45 minutes to place the tracheostomy due to soft-tissue swelling obscuring the trachea, during which time the patient became apneic, went into PEA cardiac arrest, and developed anoxic brain injury. Two months later, the patient died and the patient's family filed suit against the emergency physician, anesthesiologist, and otolaryngologist.

BACKGROUND

According to the most recent National Emergency Airway Registry (NEAR) data, intubation success rates by emergency physicians are over 99%.¹ Thus, the truly difficult intubations are infrequently faced, and the failed airway even more rare. The difficult airway exists in a patient when conventional face mask ventilation is problematic or tracheal intubation is difficult, requiring an expert with technical skill for success. Factors such as micrognathia, a short neck, a large tongue, craniofacial abnormalities, and obesity are chronic conditions associated with a difficult airway but do not inherently necessitate emergent airway management. However, conditions such as angioedema, epiglottitis, Ludwig angina,

a retropharyngeal abscess, tracheal trauma, a traumatic/expanding neck hematoma, and cervical trauma are examples of an acutely difficult airway requiring emergent management. When these patients present with dyspnea or respiratory distress, precise, immediate action is required to avert life-threatening decompensation or permanent morbid debility. Unlike other specialties, when these patients present to the emergency department (ED), we cannot postpone or cancel the case. Thus, emergency physicians must be especially astute and prepared for a rapid escalation of care and invasive management.

While difficult bag-mask ventilation and difficult intubations each occur separately in approximately 5% of patients,^{1,2,3,4} difficult bag-mask ventilation and difficult intubations occur concomitantly in much fewer patients.⁵ In fact, less than 1% of patients require a surgical airway for emergent management,⁶ likely due to the development of multiple tools for managing the difficult airway.

ANTICIPATING THE DIFFICULT AIRWAY

When patients present in extremis, a detailed history is precluded. However, several historical factors portend a difficult airway and should be rapidly determined:

1. History of oral, neck, or cervical spine surgery or irradiation.
2. History of oral or neck tumor, cellulitis, or abscess.
3. History of neck or mandibular arthritis or other joint immobility.
4. Presentation as a result of oral, facial, neck, or cervical spine trauma.
5. Use of anticoagulants or presence of a coagulopathy.



FIGURE 1-1 Interincisor gap or, for edentulous patients, “intergival gap.”

Likewise, a focused physical exam of the head and neck should be performed. The LEMON Law mnemonic has been suggested for helping direct the physical exam to determine if the patient might have a difficult airway.⁷

1. **Look externally** and assess factors associated with a difficult airway: obesity, micrognathia, a large tongue, long upper incisors, a prominent overbite with protruding maxillary incisors or underbite with large mandibular incisors, a short bull neck, poor dentition that could be dislodged into the airway, and evidence of trauma.
2. **Evaluate the 3–3–2 rule**, which states that the patient should be able to insert 3 fingers between the teeth with mouth opening (Figure 1-1), has 3 finger breadths between the front of the chin and hyoid bone (the “hyomental distance,” see Figure 1-2), and has 2 finger breadths between the hyoid bone and the thyroid cartilage (the “thyrohyoid distance,” see Figure 1-3). Patients who pass the rule (i.e., meet all of these criteria) are more likely to be successfully intubated without complications.
3. **Mallampati score assessment.** With the patient seated, mouth wide open, tongue protruding, and neck in extension, the clinician looks into the mouth to visualize the tongue, tonsils, uvula, and posterior pharynx

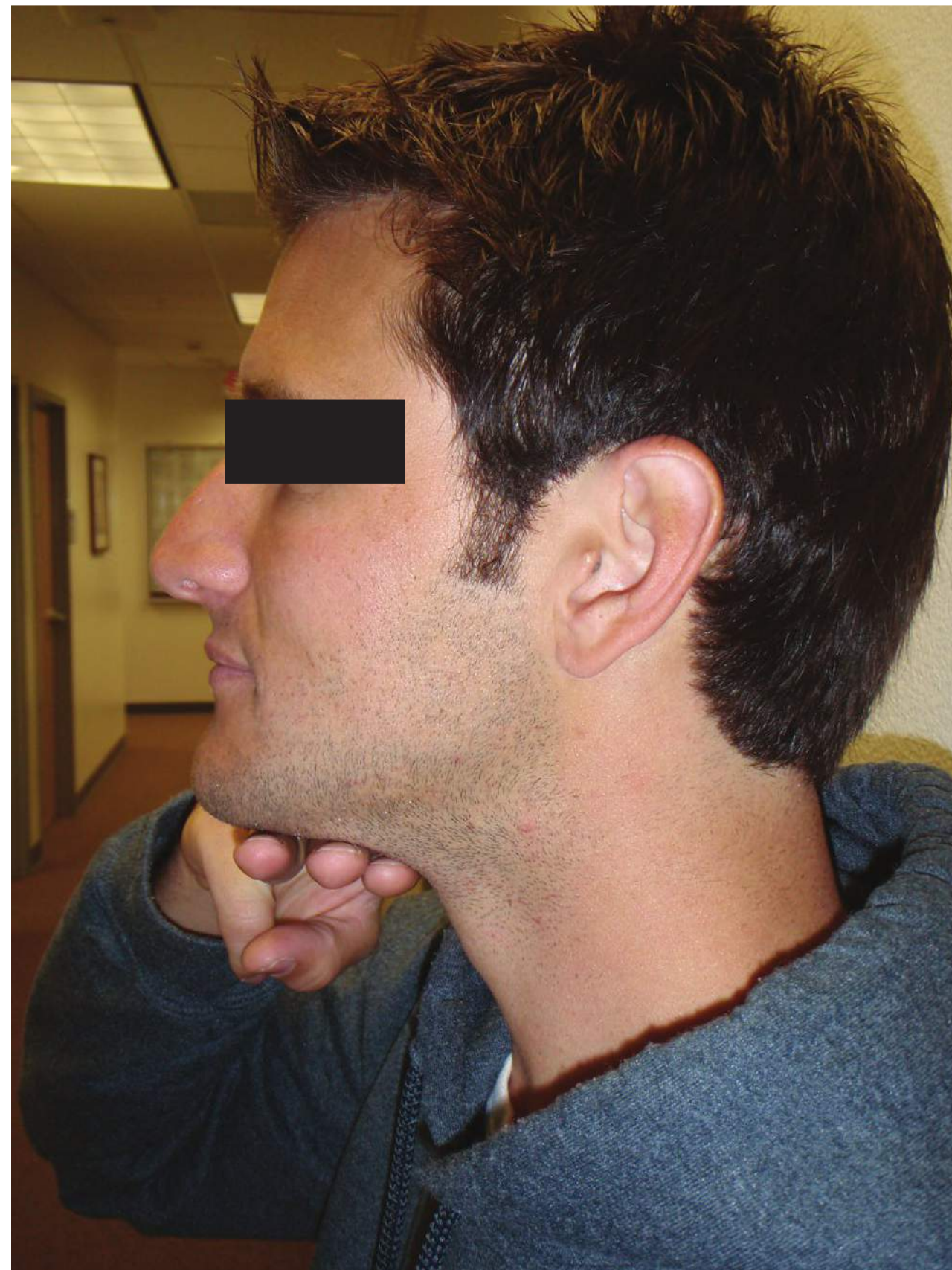


FIGURE 1-2 Hyomental distance.

(Figure 1-4). Class I airways allow for visualization of the entire posterior pharynx and tonsils, while Class II airways allow for visualization of the top of the uvula, tonsillar pillars, and soft palate. Class I and II airways are associated with successful intubations. Class III airways, however, are associated with moderate difficulty during intubation and are characterized by visualization of the soft palate only. Class IV airways, likewise, are associated with severe difficulty during intubation and do not allow for visualization of any of the posterior pharynx.

4. **Obstruction assessment.** Determine if there is an upper airway foreign body, tumor, or other obstructing factors such as epiglottitis or Ludwig angina. Three key signs to assess are difficulty handling secretions, stridor (which occurs when < 10% of normal caliber of airway circumference is clear), and a muffled voice.
5. **Neck mobility assessment.** Neck mobility directly affects a clinician's ability to visualize the vocal cords during intubation. Normal patients should be able to touch their chin to their chest on flexion with a wide range of extension. Cervical spine trauma or immobilization can limit this mobility and subsequent visualization, as can conditions such as ankylosing spondylitis and severe rheumatoid arthritis.

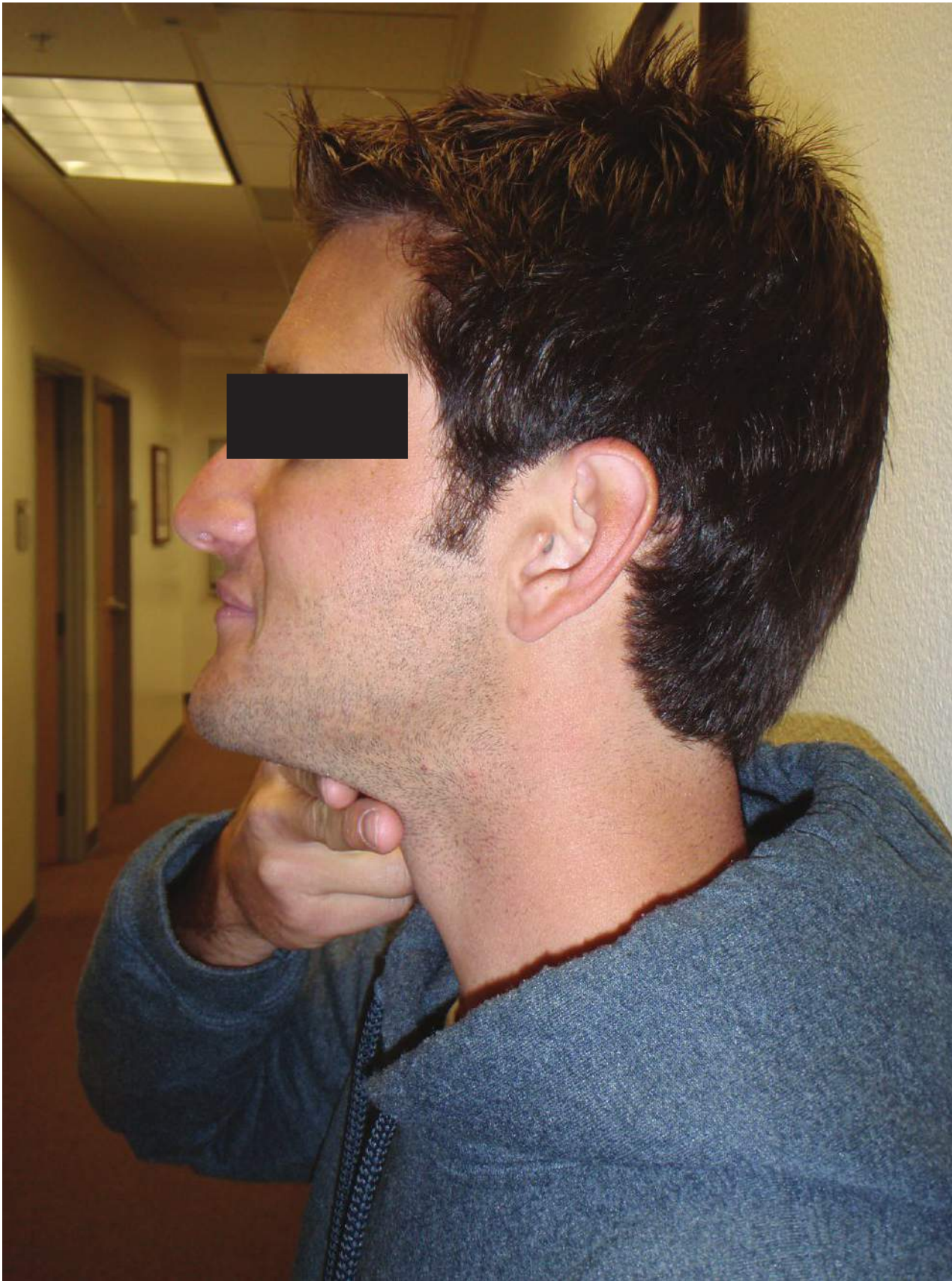


FIGURE 1-3 Thyrohyoid distance.

The MOANS mnemonic should also be used to predict those who will also be difficult to ventilate with a face mask⁷:

1. **M**ask seal should be good and not obstructed by things such as a large beard or hindered by factors such as a large bite abnormality.
2. **O**besity with either a small jaw or mid-face can prevent a good seal.
3. **A**ge > 55 years old is associated with difficult mask ventilation.
4. **N**o teeth and lack of “dental tone.”
5. **S**tiff necks can make it hard to position for proper ventilation.

PREPARE FOR AIRWAY MANAGEMENT

Once it is determined that the patient needs emergent airway management, it is important to prepare the patient, equipment, and yourself. In preparing the patient, you must provide reassurance and explain what will happen as quickly as possible. However, make every effort to do so calmly, as patient anxiety can further complicate management. Pre-oxygenate the patient in an upright position to (decrease dependent lung volume) for at least 3 minutes, if possible. If not, then have the patient take 8 vital capacity breaths to increase preintubation oxygen saturations.⁸ Passively oxygenate your

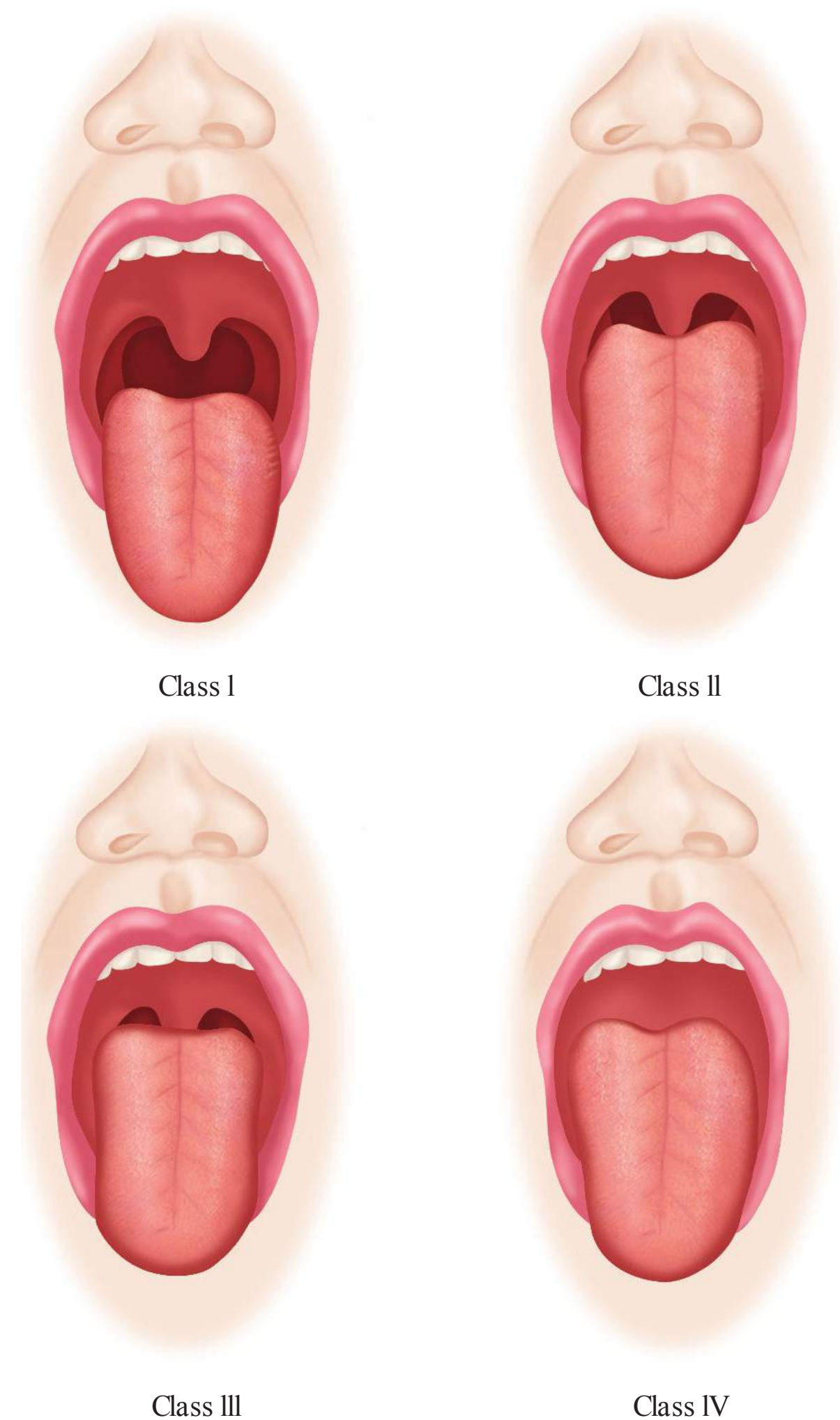


FIGURE 1-4 Mallampati grading scale for airways. Class I: Faucial pillars, soft palate, and uvula can be visualized. Class II: Faucial pillars and soft palate can be visualized, but the uvula is masked by the base of the tongue. Class III: Only the base of the uvula can be visualized. Class IV: None of the three structures can be visualized. (Reproduced with permission from Tintinalli JE, Stapczynski JS, Cline DM, et al: *Emergency Medicine: A Comprehensive Study Guide*, 7th ed. New York: McGraw-Hill Inc; 2011.)

patient during intubation with high-flow nasal cannula.⁹ This will increase desaturation time significantly through passive alveolar uptake of oxygen.⁸ Then, position the patient to align the three main axes: the laryngeal axis, the pharyngeal axis, and the oral axis (Figure 1-5). This position is referred to as “the sniffing position” or “ear to sternal notch.” This will allow for the greatest likelihood of success. While positioning the patient, make sure to check all of your equipment:

1. Do you have the right sized face mask?
2. Is the respiratory bag connected to oxygen?
3. Is suction set up and ready?
4. Is the laryngoscope in proper working order?
5. Are extra handles and blades (including various sizes and types) available?

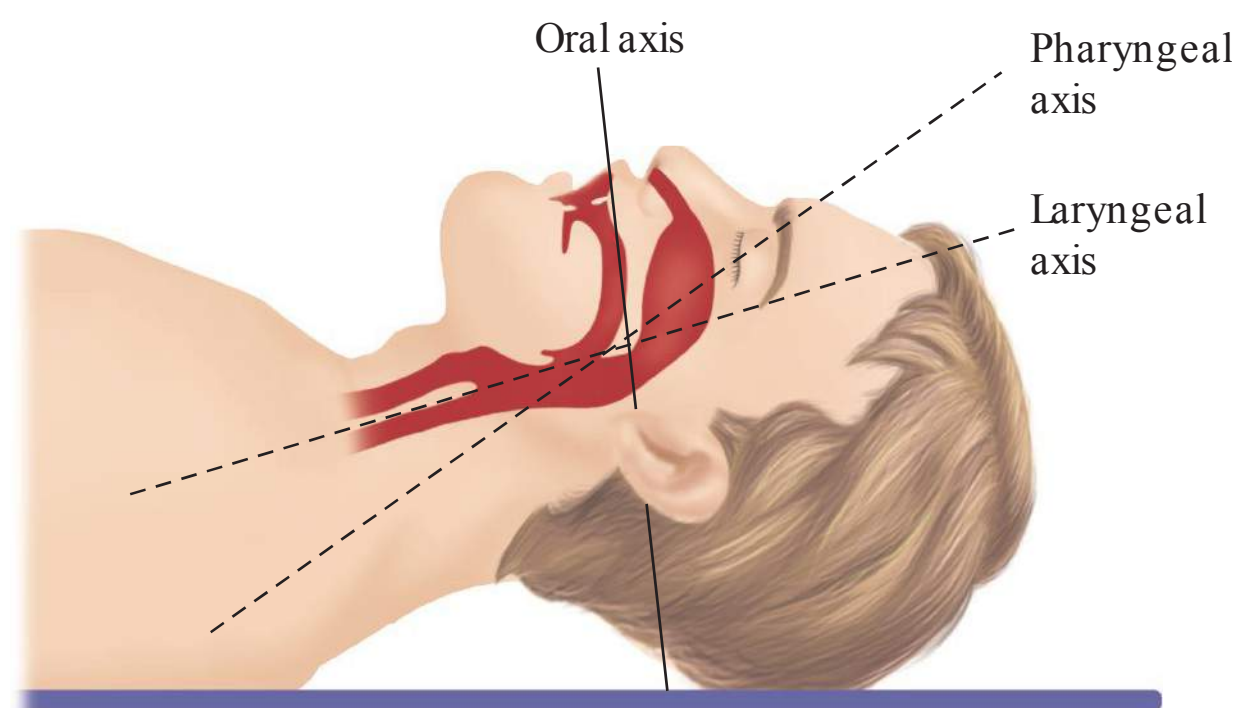


FIGURE 1-5 Proper patient position for endotracheal intubation showing oral, pharyngeal, and laryngeal axes. (Reproduced with permission from Tintinalli JE, Stapczynski JS, Cline DM, et al: *Emergency Medicine: A Comprehensive Study Guide*, 7th ed. New York: McGraw-Hill Inc; 2011.)

6. Is the end-tidal CO₂ detector or capnography ready?
7. Is your endotracheal tube (ETT) appropriately shaped and ready with both a stylet and 10 cc syringe?
8. Are multiple endotracheal tubes of different sizes available?

Then, before proceeding with intubation, make sure to think through the steps of intubation, communicate clearly with the staff regarding which medications you will use, and double check that all staff, such as respiratory technicians, know the roles they will play. Should ventilation be required before or after an initial attempt at laryngoscopy, use of a PEEP valve on your bag valve mask will sustain alveolar distention. This, along with low volumes (6–7 mL/kg) and a low rate (6–8 breaths/min), will maximize efficiency of bagging.

OROTRACHEAL INTUBATION MANEUVERS

In the event that you are unsuccessful with your initial intubation attempt, you should immediately consider several maneuvers to improve the likelihood of successful orotracheal intubation:

1. Reposition the patient to properly align the airway axes.
2. Consider larynx manipulation whereby you gently manipulate the thyroid cartilage with your right hand, providing gentle backward, upward, rightward pressure. If you visualize the vocal cords, an assistant can hold the thyroid cartilage in that position for you to proceed with intubation. This is associated with improved visualization of the glottis and subsequent successful intubation.⁷
3. Try a different laryngoscope blade. Sometimes, simply changing the size of your laryngoscope blade will lead to a successful intubation. Other times, you may need to change from a Macintosh blade to a Miller blade. While the Macintosh blade is preferred by most clinicians, it can be difficult to use in patients with a large

or floppy epiglottis, in which case a Miller blade can be used to obtain better visualization of the vocal cords.

4. Try using a smaller ETT. Sometimes, due to the patient's habitus or size, you may not be able to advance a large sized tube and simply changing to a smaller size will lead to a successful intubation.
5. Finally, if you have the option, consider having a different clinician attempt the intubation.

While these maneuvers are being attempted, you should also be preparing to move on to another airway tool to facilitate airway control and ensure proper ventilation. Unless these methods are practiced under conditions similar to actual intubation, the stress of a decompensating patient can make them difficult to perform when needed most. I suggest that clinicians master two or three of these “rescue” tools for use in the emergent setting.

Video Laryngoscope

One of the easiest difficult airway tools to use is the video laryngoscope (Figure 1-6). It has been shown to improve glottic visualization and, thus, success of intubation attempts.¹⁰ Finally, video laryngoscopes are, for all intents and purposes, the current standard of care. To use a video laryngoscope, once the patient is positioned and the mouth opened, place the laryngoscope midline in the posterior pharynx. When using the video laryngoscope, the tongue does not need to be manually displaced as with traditional laryngoscopy. Then, rather than looking into the pharynx, the clinician looks at the video monitor while advancing the laryngoscope to identify the epiglottis and then the vocal cords. Upon visualization of the glottis, the ETT is placed into the pharynx



FIGURE 1-6 Video laryngoscope.

under direct visualization before advancing it into the trachea through the vocal cords under video screen visualization.

This approach is easy to learn, because the manual technique is similar to orotracheal intubation with traditional laryngoscopy and direct visualization. Furthermore, this technique has been associated with improved visualization of the glottis¹⁰ and appears to be the most easy difficult airway tool to learn.

Be aware that there are rare circumstances in which indirect video laryngoscopy will not be possible, such as equipment failure, copious secretions, or a bloody airway. Because of this, and despite the high success rate of video laryngoscopy, it is vital to maintain direct laryngoscopy skills throughout your career.

LIGHT WAND

The light wand (Figure 1-7) is another option for the intubation of patients with a difficult airway, especially when direct visualization is hindered due to trismus or obscuration due to copious secretions or bleeding. It involves intubation without direct visualization of the epiglottis or vocal cords, which is disconcerting to some clinicians. However, it can be more successful than traditional intubation under direct laryngoscopy and may be used to rescue failed attempts.^{12,13}

The light wand is a semi-rigid stylet with a light on the end (Figure 1-8). With the patient positioned for intubation, the light wand is turned on and placed in the posterior pharynx, then slowly advanced while the clinician observes the anterior exterior neck for evidence of the light “shining” through the skin. It is important to note that the stylet is advanced without direct visualization of the pharynx or glottic structures. When the stylet is placed in the trachea, the light shines distinctly through the skin due to the thin tracheal membranes that allow for the transmission of light. Upon visualization of this light in the anterior midline of the neck, the endotracheal tube can be advanced followed by confirmation of appropriate tube placement using standard technique. If the stylet is placed in the esophagus, the light is either not seen or perceived as a diffuse “glow” rather than a



FIGURE 1-7 Lighted stylet (e.g., Trachlight, Surch-lite).

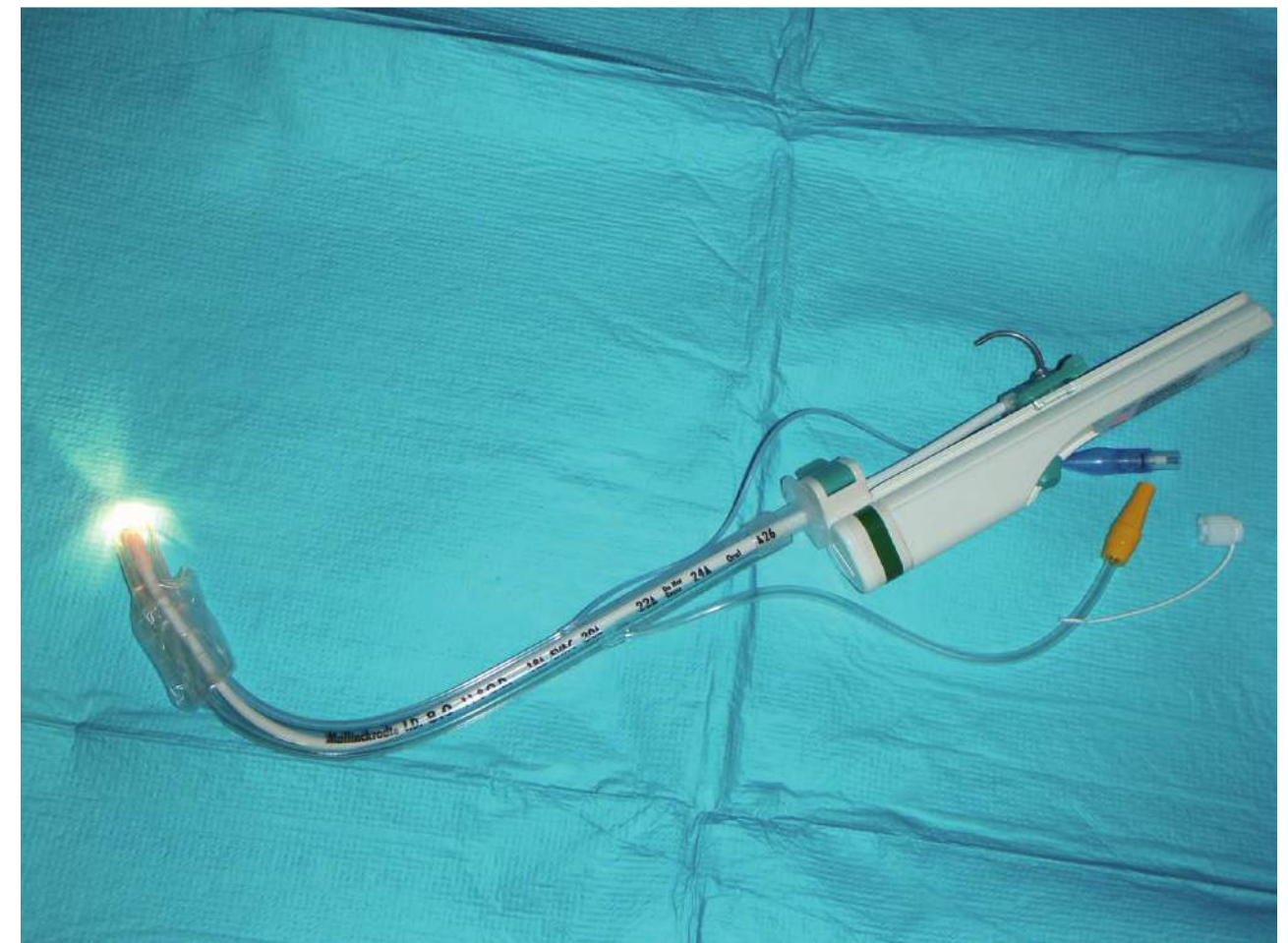


FIGURE 1-8 Lighted stylet, a semi-rigid stylet with a light on the end.

distinct point of light, in which case the clinician must reposition the stylet until a distinct point of light is seen shining in the anterior midline of the neck.

Although the light wand has been used as a rescue airway technique, it requires transillumination of the trachea and anterior neck, which is hindered by patient body habitus, skin color, or when there is too much ambient light. Therefore, one should consider potential limitations due to body habitus as well as dimming the lights when performing this technique. Furthermore, clinicians must practice using the light wand under controlled settings before emergent use since it is associated with an appreciable learning curve, whereas novice clinicians find direct laryngoscopy to be more effective.¹⁴

INTUBATING INTRODUCER

The intubating introducer (e.g., Eschmann Introducer, SunMed Flex Guide, and Frova; Figure 1-9) is a semi-rigid, long stylet (typically > 60 cm) with a bent, soft tip designed



FIGURE 1-9 Intubating introducer (e.g., Eschmann Introducer, SunMed Flex Guide, and Frova).

for use with anterior airways or the situation when direct visualization of the glottic structures is not possible (e.g., significant bleeding from trauma). In the past, the term “bougie” was used to refer to such introducers because a bougie dilator was used as one of the first introducers. The Frova is a particular intubating introducer that also has a fenestrated tip to allow oxygenation when used with an adapter and bag-valve aperture.

The introducer is best used on patients in whom a full glottis view is not possible. The idea is to obtain the best view possible (often the base of the arytenoids can be seen), then the intubating introducer is placed in the posterior pharynx and slowly advanced towards the trachea, maintaining the bent tip in a midline, anterior-most position. The introducer is advanced until two tactile sensations are appreciated, confirming placement in the trachea. The first is the feeling of the tracheal rings, which are appreciated as “vibrations” or “clicks” by the clinician. The second is resistance to further advancement, corresponding with arrival at the smaller airways (as opposed to the esophagus, which would continue to the stomach without resistance). Once tracheal placement is confirmed, the ETT is advanced using a Seldinger technique with confirmation of appropriate placement using standard technique.

The advantages of this technique include use in the case of anterior airways and those with obscured direct visualization, potential for use with or without laryngoscopy, and ease of use by novice clinicians.¹⁴ On the other hand, it may be difficult to use in cases of tracheal trauma and may be relatively contraindicated in cases of angioedema in which increased edema may result from the triggering of the bradykinin/complement cascade.

FIBEROPTIC STYLETS

Fiberoptic stylets (FOS; e.g., Shikani Optical Stylet, Bonfils Retromolar Intubation Fiberscope, Levitan FPS scope; Figure 1-10) include a fiberoptic lens or camera chip at the distal end of a metal stylet, designed to move the clinician’s

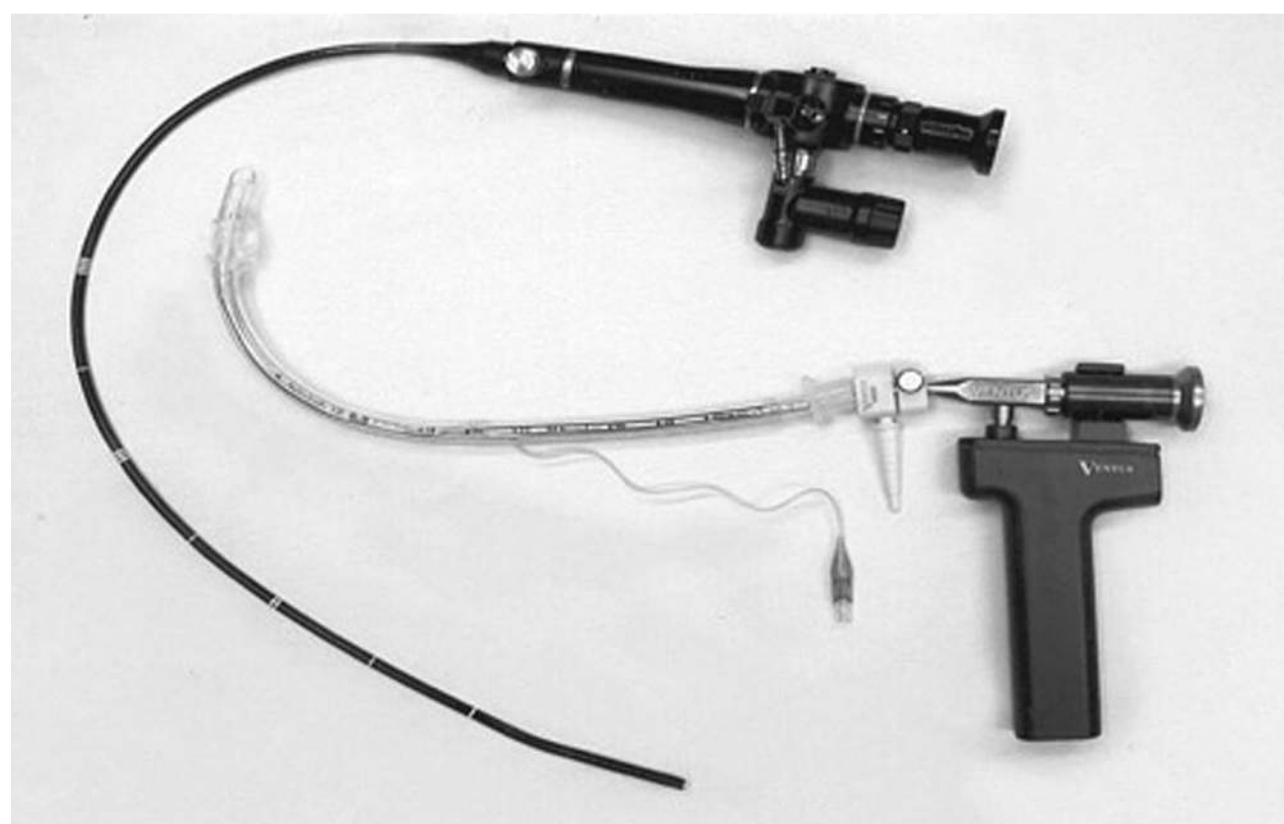


FIGURE 1-10 A fiberoptic laryngoscope and a Shikani endoscope (Used with permission from Clarus Medical LLC, Minneapolis, MN).

view from the mouth and posterior pharynx to the end of the FOS near the glottis. They can be rigid or semi-rigid.

FOS intubation is facilitated by using a laryngoscope to elevate the tongue from the posterior oropharynx. The FOS is placed into the oropharynx along the teeth or gum line. Using the teeth as a guide, you advance the wand until you pass the last molar. At this point you turn the FOS inward, where you will usually be able to see the vocal cords or epiglottis. You then advance the FOS toward the trachea while visualizing the pharyngeal anatomy through an eyepiece or screen. Once the vocal cords are visualized, the stylet is advanced into the trachea and a preloaded ETT is advanced over the stylet with confirmation of appropriate placement using standard technique.

The advantages of this technique include use in the case of anterior airways, potential for use with or without laryngoscopy, and cost, typically thousands of dollars less than a video laryngoscope. Limitations include inability to use when copious secretions or blood is present, a moderate learning curve, and, finally, while cheaper than a full video laryngoscope, a FOS is still more expensive than a standard laryngoscope.

FLEXIBLE BRONCHOSCOPE

Flexible bronchoscopes are flexible, directable fiberoptic tools that allow for visualization of the airway anatomy with greater manual control than possible with a fiberoptic stylet. Unfortunately, the time required for set up and possibility of scope damage from patient biting or mishandling limit the use of flexible bronchoscopes for rapid, emergent orotracheal intubation. However, when there is time to prepare for a semi-awake nasotracheal or orotracheal intubation, flexible bronchoscopes can be invaluable. This could be especially useful in patients with suspected epiglottitis, angioedema, or severe obstructive sleep apnea in which traditional intubation would be difficult and a surgical airway challenging. It is better tolerated by patients and allows them to remain sitting up. Nasal intubations should be performed with a pediatric bronchoscope as the smaller diameter tube is better tolerated by patients.

The patient can be prepared by administering intranasal lidocaine followed by (or in conjunction with) phenylephrine or oxymetazoline. These can be delivered via atomizer or nebulizer. Using a nebulizer can facilitate delivery deeper into the oropharynx, but should be delivered at 5 L/min as opposed to the standard 15 L/min. The higher flow delivers the majority of the medicine to the lungs rather than the name and oropharynx. Once the patient is anesthetized, you can assist placement of the bronchoscope above the vocal cords by using either a nasal trumpet or a 6.5 ETT lubricated with lidocaine jelly into the nare. The nasal trumpet must be split lengthwise, allowing you to peel it off of the scope once it is properly placed. On rare occasions, the patient’s nare may be too small to facilitate ETT passage. To avoid this, you can use the ETT as your nasal trumpet.

Be cautious when placing this into the nare as the ETT is much more rigid than a nasal trumpet, so has a higher incidence of causing epistaxis. With the patient sitting upright,

the flexible bronchoscope can be advanced through the lumen of the tube into the posterior pharynx. From there, the flexible bronchoscope is advanced while visualizing the epiglottis and vocal cords with the eyepiece or screen. If there is significant edema or when getting close to the vocal cords, only advance your scope when the patient is breathing in. This opens up both the vocal cords and the surrounding oropharynx, and is a vital reason to perform these intubations awake. If at any point you lose your spatial orientation or can only see tissue, slowly back the scope out until you see landmarks that you recognize. Once the distal tip of the scope passes through the vocal cords, the ETT is then advanced, the scope removed, and placement confirmed using standard technique. If there is difficulty advancing the ETT into the trachea (it may be caught on the arytenoids), rotating the flexible bronchoscope counterclockwise may overcome the obstruction and allow for advancement of the tube. Once your ETT placement is confirmed, immediately sedate your patient, but be cautious that you have plenty of help to restrain the patient before, during, and after sedation.

The main advantages of this technique are use with anterior airways, improved visualization, and ability to be performed in upright patients able to breathe on their own. The main disadvantages are cost, time (typically 15–20 minutes), the need for greater operator/clinician skill, and need for clear visualization which can be obscured by secretions, hemorrhage, and obstructing masses.

RETROGRADE WIRE INTUBATION

While rarely done when the other methods for tracheal intubation have failed, the physician may opt for a retrograde wire intubation. This should be rapidly attempted while preparing for placement of a surgical airway. The anterior neck should be quickly prepped with betadine or Chloraprep, followed by rapid identification of the cricothyroid membrane (Figure 1-11). Then an 18-gauge needle should be placed through



FIGURE 1-11 Locate the cricothyroid membrane. (Used with permission from Jennifer McBride, PhD and Michael Phelan, MD, Cleveland Clinic and Michael Smith, MD, MetroHealth.)

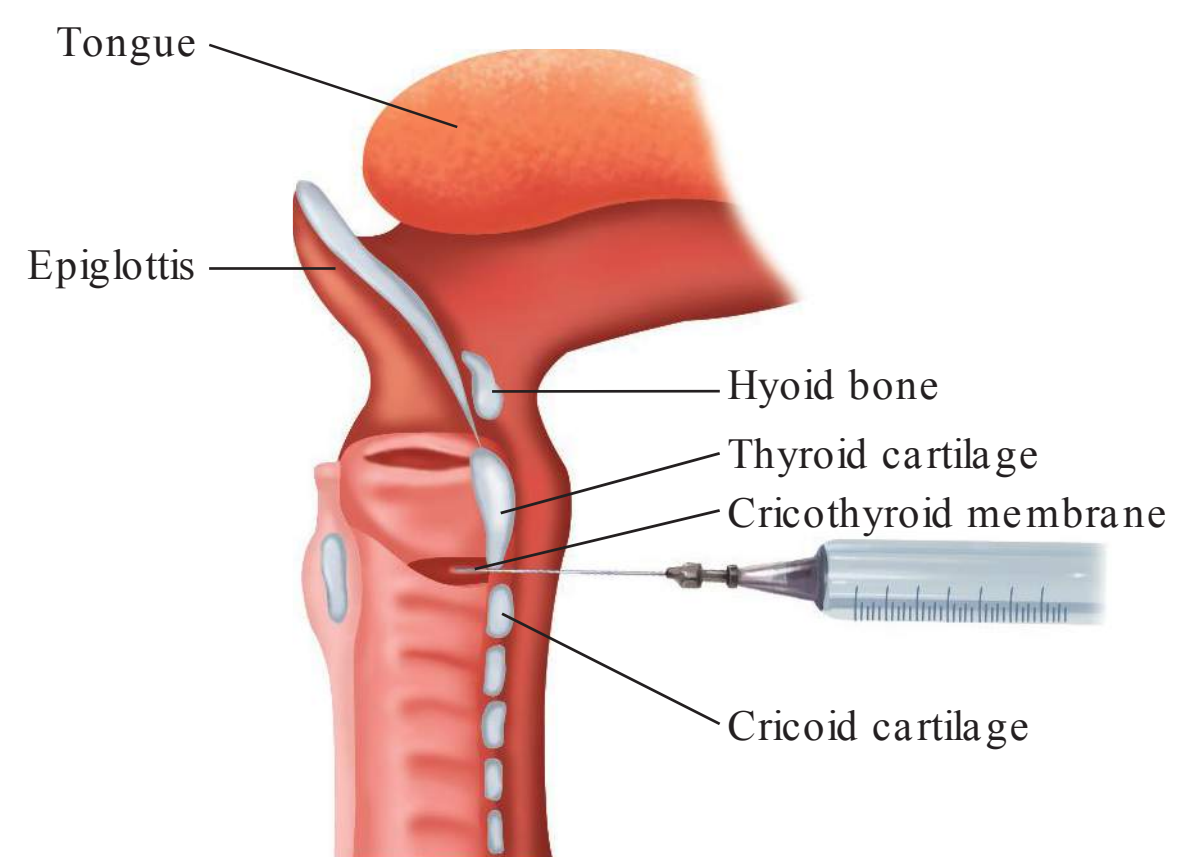


FIGURE 1-12 Translaryngeal anesthesia via cricothyroid puncture. Anatomy, cross-sectional view. Same landmarks as those for translaryngeal ventilation. Lateral view. (Reproduced with permission from Tintinalli JE, Kelen GD, Stapczynski JS: *Emergency Medicine: A Comprehensive Study Guide*, 6th ed. New York: McGraw-Hill Inc; 2004.)

the cricothyroid membrane (Figure 1-12) with the placement confirmed by aspiration of air, and the needle repositioned aiming cephalad. A guide wire can then be advanced through the needle into the oropharynx, where Magill forceps or alligators can be used to extract the distal tip of the wire out of the mouth. Once the distal tip is obtained and firmly grasped, an ETT can be advanced over the wire into the trachea with a Seldinger-like technique and placement confirmed using standard measures.

This technique often requires two operators—one at the neck and one at the mouth—and is invasive, but has less morbidity than a surgical airway when successful. However, it can be difficult, especially in patients with upper airway obstruction or poor visualization due to blood or secretions.

Ultrasound

Although never studied in the setting of the emergent difficult airway, ultrasound can help localize the tracheal rings and cricothyroid membrane. This may facilitate retrograde wire intubation by directing needle placement and confirming tube placement. In addition, when possible, a second operator can use ultrasound to confirm placement of the light wand, intubating introducer, or FOS in the trachea prior to advancing the ETT.

Failed Tracheal Intubation

When the clinician is unable to perform tracheal intubation for the patient requiring emergent airway management, several tools can be used to provide oxygen while preparing to place a surgical airway (e.g., cricothyrotomy or emergent tracheostomy; see chapter 3 “Emergency Surgical Airway”). However, as none of these provides definitive airway management, they should only be used to bridge patients to a definitive airway.



FIGURE 1-13 Laryngeal mask airway (LMA).

Laryngeal Mask Airway (LMA)

The LMA (Figure 1-13) is often used by anesthesiologists in the controlled setting of the operating room for elective cases, but it is not ideal for emergent settings because it does not protect the airway from secretions, aspiration, blood, or mass lesions such as expanding hematomas. Furthermore, the LMA is ineffective in situations in which there is an obstruction (e.g., epiglottitis, angioedema, tracheal trauma) and should not even be attempted in such cases. The LMA works by creating a seal over the larynx with a soft mask that allows for oxygen to be blown into the lungs, in a sense moving the bag-mask apparatus from the level of the mouth to the larynx.

The LMA is inserted “backwards” into the posterior pharynx and then advanced while being rotated forward, seating the LMA in the hypopharynx. Once this is done, the cuff is inflated and bag ventilation can be performed. Even if adequate oxygenation and ventilation can be provided with an LMA, the clinician must remember that this is not a definitive airway because the patient’s airway is not protected from secretions, aspiration, blood, or mass lesions such as expanding hematomas. The LMA should only be used emergently to provide oxygen while preparing to establish a definitive airway.

An intubating LMA (I-LMA) is a specific type of LMA with an aperture in the mask that allows for passage of an ETT through the LMA into the trachea. The I-LMA is designed so that the tube aperture is above the glottis in most patients when the mask is seated in the hypopharynx. Thus, once the I-LMA is placed, a flexible ETT can be blindly passed through the lumen into the trachea with confirmation by standard technique. Intubation with an I-LMA can be facilitated and/or confirmed with a flexible bronchoscope after placement. The I-LMA will frequently fail in cases of altered anatomy or glottic obstruction.

Combitube or King Airway

While infrequently used in EDs or ICU, Combitubes and King Airways are often used by EMS systems. The



FIGURE 1-14 Combitube and King Airway.

Combitube and King Airway (Figure 1-14) are dual-port, double-cuffed tubes designed for use in the difficult airway. They are placed blindly into the posterior pharynx and advanced, presumably into the esophagus. Once the tube is placed in the esophagus, the distal cuff lies in the esophagus and the proximal cuff lies in the supraglottic space. The distal cuff is inflated to prevent air from entering the stomach and help block stomach contents from aspirating into the airway. The proximal cuff is inflated to prevent air from leaking out of the mouth and help block secretions from falling back into the trachea. Oxygen can then be bag ventilated from the laryngeal port through laryngeal fenestrations that lie above the glottic opening between the two cuffs.

As with the LMA, even if adequate oxygenation and ventilation can be provided with a Combitube or King Airway, the clinician must remember that this is not a definitive airway because the patient’s airway is not fully protected from secretions, aspiration, blood, or mass lesions. Unlike the LMA, there is no “intubating” version and, therefore, the Combitube or King Airway should only be used emergently to provide oxygen while preparing to establish a definitive airway. The only exception is on the rare occasion when the tube is placed blindly in the trachea, in which case the pharyngeal port can be used to ventilate the trachea since it is continuous with the distal tip of the tube and essentially functioning as an ETT.

Needle Cricothyrotomy

In the event that the clinician is unable to perform tracheal intubation and cannot provide oxygen through an LMA, Combitube, or King Airway, supplemental oxygen may be provided emergently via needle cricothyrotomy. However, by the time this is attempted, the clinician only has a few minutes in which to establish a surgical airway.

Once the anterior neck is prepped with betadine or Chloraprep, the cricothyroid membrane should be rapidly identified (Figure 1-11). Then, an 18-gauge needle should be

placed through the cricothyroid membrane (Figure 1-12), which can be confirmed by aspiration of air using a 30-cc syringe. Once this is done, remove the plunger, fasten an ETT connector to the open end of the syringe, and attach a respiratory bag. Then, using positive pressure, oxygen can be bagged through the needle (jet ventilation) into the lungs while preparing for a surgical airway to follow (see chapter 3 “Emergency Surgical Airway”). Note that jet ventilation oxygenates, but does not exchange CO₂.

Summary

Clinicians can anticipate encountering a difficult airway 1% to 5% of the time and should be able to rapidly assess the likelihood of a patient have a difficult airway based on a directed history and physical exam. In the event that a patient has a difficult airway and requires emergent management, a number of maneuvers can be done to facilitate successful orotracheal intubation by traditional laryngoscopy. When these fail, clinicians should be familiar with available “rescue” devices and techniques to provide oxygenation and ventilation without the morbidity associated with a surgical airway. It is vital that clinicians become familiar with these rescue devices in settings outside of the difficult airway.

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Physiology of the Peri-Intubation

Zachary Ginsberg • Scott D. Weingart

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Airway management is one of the most time-critical interventions in intensive care. If any difficulty delays or prevents ideal airway management, the patient is exposed to severe risk. Most texts place heavy emphasis on the prediction of anatomical difficulties. Additionally, considerable focus is provided on the steps of physically placing an endotracheal tube.

However, the difficulties posed by a patient's underlying physiology is where many of the pitfalls lie in critical care airway management. The decision to intubate a patient emergently indicates that patient is *in extremis*, and so particular attention to the patient's physiologic reserve and potential response to induction options should hold equal importance in the process of intubation as technique and tools.

Upon the decision to intubate, it is crucial to assess the patient's physiologic reserve and, while preparing, take steps to optimize the patient's chances of making it through the intubation process without decompensation. This chapter outlines several key considerations in the approach to the physiology of the peri-intubation period in the crashing patient.

Broadly, the factors that lead to the difficult physiologic intubation can be broken down into three categories: hemodynamics, oxygenation, and pH (acidosis). When ignored, each can lead to devastating consequences. As airway texts gravitate towards acronyms, these factors can be encompassed by the mnemonic "*HOp* killers."

HEMODYNAMIC ISSUES

A patient who is hypotensive prior to intubation is at high risk of further hemodynamic decompensation or cardiac arrest during the peri-intubation period.¹⁻² Cognizance of this risk and careful selection of induction agent can significantly impact a patient's likelihood of surviving the intubation. The highest priority is to keep the patient alive; all other concerns are secondary to this goal. Amnesia, analgesia, and a lack of awareness are imperative, but should not be prioritized above preserving hemodynamics until a definitive airway is in place.

Every induction agent will lower an already hypotensive patient's blood pressure due to the loss of the patient's catecholamine surge. During critical illness, the "fight or flight" mode supplies endogenous surges of catecholamines. Induction will blunt this surge as we shut off the central stress response. Preload, and therefore cardiac output, are further augmented by large tidal volumes generated by negative inspiratory force. The switch to positive pressure ventilation can reduce preload and worsen hypotension.

INDUCTION AGENTS

In the case of propofol, markedly reducing the dose of propofol by 90% can facilitate induction without causing

such exaggerated hemodynamic effects. These reduced doses when administered to shock patients seem to still retain the central sedating effects of full doses.^{3,4}

Etomidate intrinsically does not cause hemodynamic effects, but it does cause the same removal of catecholamine drive.^{5,6} As opposed to propofol, the dose of etomidate should not be reduced, and may even require a larger dose when given to a patient in a shock state. Additionally, etomidate does not provide analgesia, and given a variable metabolism in a shock state, may not be the first-line induction agent of choice.

In general, midazolam, with or without fentanyl, is a poor choice for a hemodynamically unstable induction. The onset of action occurs at approximately 5 minutes in patients with poor cardiac output, which means that sedation and analgesia are only provided post-induction, and any possible amnestic properties will rely on retrograde amnesia. Providing midazolam several minutes prior to induction may offer amnestic properties, but it also may cause unwanted hemodynamic effects while still in the preparatory stages of intubation.⁷

For the hemodynamically unstable airway, ketamine offers a drug profile which may be optimal.^{4,8–10} Ketamine has a range of doses from low-dose analgesic (0.1–0.2 mg/kg) to full dissociative dosing (1–2 mg/kg) used for airway induction. The challenge in the setting of hypotension is that the full dissociative dose may cause loss of endogenous sympathetic tone. While ketamine offers intrinsic sympathetic augmentation, it is by no means as potent as the endogenous stressors running through the shock patient's body. Thus a middle-range dose may be ideal in the hemodynamically unstable patient.^{11,12} In particular, this approach provides potent analgesia and partially dissociates the patient to better tolerate the placement of a laryngoscope while maintaining, and perhaps augmenting, sympathetic tone. Ketamine also has one of the quickest onsets of action—crucial in patients with poor cardiac output.

Concerns regarding ketamine's elevation of intracranial pressure (ICP) have turned out to be false. In fact, recent studies have exonerated ketamine as a cause of increased ICP.¹³ Of course, in a different patient population, such as the intracranial bleed patient with elevated blood pressure, ketamine's blood pressure augmentation may increase the ICP due to lack of autoregulation. This is not an issue in the hypotensive patient. A summary of the dosing and considerations for these agents is included in Table 2-1.

PARALYTICS

Paralytics in the hypotensive patient take longer to work due to increased circulation time; however, a higher dose can overcome this problem.¹⁴ Succinylcholine dosed at 2 mg/kg or rocuronium dosed at 1.6–1.8 mg/kg are appropriate doses to attempt to match the 45- to 60-second onset time seen in hemodynamically stable intubations.¹⁵

HYPOTENSIVE INDUCTION AS PERFORMED BY THE AUTHORS

The following protocol is used by the authors when intubating the hypotensive patient. Scopolamine 0.4 mg IVP is used as a pretreatment 5 minutes prior to intubation and has potent amnestic effects with no negative hemodynamic consequences. Ketamine at 0.5 mg/kg is chosen for induction. Succinylcholine at 2 mg/kg or rocuronium given at 1.6 mg/kg are used for muscle relaxation at the higher doses required for a hypotensive state.¹⁵

OTHER INTERVENTIONS

Anticipating some loss of blood pressure on induction, the practice of loading with crystalloid in the septic patient or blood products in the trauma patient can augment preload and provide some reserve. In the patient with distributive shock, initiating vasopressors, if possible, before intubation can provide a buffer of safety during induction.

Bolus doses of vasopressors should be at hand and may be considered to forestall cardiovascular collapse in the peri- or post-intubation period.¹⁶ Epinephrine in this context may be preferable to phenylephrine because it offers beta-1 augmentation that provides for a more rapid onset of intubation medications via increased cardiac output.⁵

The lability of the patient's blood pressure in response to positive airway pressure should be carefully guarded against in the immediate post-induction period. Preload reduces in the face of positive pressure. Ventilator pressures and positive-end-expiratory-pressure (PEEP) should be started on lower settings and titrated up as needed. Volume augmentation or vasopressor support can mitigate these effects, but may require some time before the patient responds.



TABLE 2-1: Commonly Used Induction Agents

Drug	Induction Dose	Adjusted Dose	Considerations
Propofol	1–2 mg/kg	0.1–0.2 mg/kg	Lowers blood pressure
Ketamine	1–2 mg/kg	0.5–1 mg/kg	Raises stroke volume and heart rate Stable metabolism
Etomidate	0.3 mg/kg	Higher dosing	No analgesic effect
Midazolam	2–4 mg	Lower dose	Provides retrograde amnesia but prolonged onset in hypotension

OXYGENATION ISSUES

When the patient is hypoxic prior to intubation, the astute clinician recognizes the patient's poor tolerance for apnea during induction and takes steps to improve oxygenation prior to induction. These steps include increasing the delivery of oxygen and recruitment of unused alveoli to improve gas exchange. Understanding how to use the tools available can help achieve optimization prior to induction.

PREOXYGENATION

Typical teaching for rapid sequence intubation is to use a 100% non-rebreather mask for preoxygenation. Unfortunately, this device no longer is sold and the item we conflate with a 100% non-rebreather is actually a reservoir face mask capable of providing only 60% FiO₂. The placement of a nasal cannula at 15 lpm underneath this pseudo-non-rebreather can provide a > 90% FiO₂. Using this combination, three minutes of tidal volume breathing or eight vital capacity breaths (maximal inhalation and exhalation) is sufficient to achieve washout of nitrogen. The optimal positioning is semi-Fowler with the head at a slight angle of 20 to 30 degrees to improve preoxygenation and glottic exposure. In the hemodynamically normal, non-physiologically shunted patient, the time to hemoglobin desaturation to 90% can be up to eight minutes.¹⁷ However, in critical care we rarely see these extended times until desaturation, as many of these patients have underlying hemodynamic and pulmonary pathology.

FAILURE TO RESPOND ADEQUATELY TO STANDARD PREOXYGENATION

If a patient does not achieve a saturation of $\geq 95\%$ with these techniques, physiologic shunt is inevitably the cause. Attempts to reverse the underlying physiologic drivers may provide an increase in the time until desaturation during the patient's apneic period.

Physiologic shunt arises from inability for oxygen to flow into alveoli due to atelectasis, blood, pus, or fluid. When blood flows past the obstructed alveolus, it returns to the systemic circulation without picking up additional oxygen molecules. No matter how much oxygen a provider administers, it will not improve oxygen saturation in the presence of a shunt because the oxygen itself is unable to reach the physiologically relevant alveolar-capillary interface.

The short-term solution entails increasing the mean airway pressure to stent open and recruit additional alveoli. Bag-valve-mask (BVM) ventilation or volume control ventilation without augmented end-expiratory-pressure does not improve shunt because they provide only intermittent periods of heightened pressure through the airway. Any recruited alveoli opened during the positive-pressure breath immediately de-recruit between breaths. Instead, patients need to increase the space between either negative or positive pressure breaths above an end-expiratory pressure of zero. PEEP

provides the optimal quick and readily available solution to oxygenation problems of shunt physiology.

Delivery of PEEP or continuous positive airway pressure (CPAP) recruits these shunted airways and expands the surface area available for oxygen diffusion across the alveolar-capillary interface. This recruitment maneuver in the preintubation preoxygenation period may improve the patient's reserve and extend the time interval until desaturation during the intubation process. Of note, PEEP settings over 18 to 22 cm H₂O may result in gastric insufflation, so by convention, PEEP for preoxygenation should remain below 15 cm H₂O.

Administration of PEEP requires the ability to rapidly place patients on CPAP in the ED prior to intubation to improve preoxygenation while setting up the equipment for intubation. If this is unavailable, a PEEP valve attached to a BVM, held with a good seal around the nose and mouth, can provide a cheap and easily accessed source of PEEP. It should be noted that, unless squeezed actively, many BVM devices only deliver room air. As the patient inspires, the resistance to flow is lowest from the nonvalved exhalation port rather than from the reservoir. This results in the patient breathing room air rather than oxygen unless the BVM device has a pair of one-way valves, which is uncommon, or a PEEP valve. Since the PEEP valve blocks the exhalation port of the BVM, the pathway of least resistance for inhalation becomes the oxygen reservoir and increases the FiO₂ delivered during spontaneous breaths to 100%. Without a PEEP valve, the BVM should not be used to preoxygenate a patient who is spontaneously breathing. Stand-alone CPAP face masks are also commercially available.

APNEIC OXYGENATION: PREVENTING DEOXYGENATION DURING PARALYSIS

Oxygenation occurs predominantly through the passive diffusion across the alveolar-capillary membrane. In a period of apnea without the inhalation of oxygen, as occurs with paralysis, the alveolar partial pressure of oxygen (pAO₂) declines. The administration of supplemental oxygen without administering breaths can maintain oxygen levels for considerable time. This occurs because oxygenation is not dependent on breaths or tidal volume; rather, as the pAO₂ decreases, it draws the oxygen down the trachea-bronchial tree through a small amount of negative pressure. The addition of nasal cannula at 15 lpm can replenish the oxygen within the oropharynx, allowing a continuous reservoir for apneic oxygenation, and extending the time prior to desaturation.

PH ISSUES: PROFOUND ACIDOSIS AND VENTILATORY FAILURE

In a patient with profound metabolic acidosis, a survivable pH is often maintained via respiratory compensation. As these patients become obtunded, their compensation declines. It is usually at this physiologically tenuous point that we make the

decision to intubate. Any period of apnea during the intubation process could result in further increase of carbon dioxide, worsening pH and, in turn, leading to cardiac arrest.

Attempts to temporize this situation with sodium bicarbonate ignore the fact that this drug buffers by creating additional CO_2 . This additional CO_2 worsens the typical physiologic situation of the patient who requires emergent intubation, in whom the inability to adequately eliminate CO_2 through adequate ventilation is the reason for intubation in the first place.

The better method is to address the carbon dioxide directly. First, if the patient is still spontaneously breathing, augmentation of each breath may be helpful in the intubation preparation period. Placing the patient on non-invasive positive pressure ventilation with inspiratory pressure may help the patient regain respiratory compensation in preparation for induction. IPAP settings of 10 to 15 cm H_2O are generally used. Placement of ETCO_2 monitoring allows the determination of a preinduction baseline and becomes the goal in the post-intubation period.

While the provision of positive-pressure breaths is usually avoided during rapid sequence intubation, in this case they are essential. Providing 6 to 8 low-volume, low-pressure breaths during the apnea period strikes the balance between CO_2 rise and the avoidance of gastric insufflation. First-pass success is essential as the physiologic reserve of the patient is critically low and the shortest interval of apnea while passing an endotracheal tube is critical.

When considering the proper rate and volume to ventilate the now intubated patient, consider the following: A minute ventilation of 60 cc/kg/min maintains eucapnea in a non-intubated patient. With intubation, the addition of the dead space of the tubing requires 100 to 120 cc/kg/min to maintain normal PaCO_2 . In a profoundly acidemic patient, reducing carbon dioxide is key, so the goal is 200 to 240 cc/kg/min. An 8 cc/kg tidal volume at 30 breaths/minute is a good starting point in these patients. The next step is a confirmation that the ETCO_2 is at least as low as preintubation values. A venous or arterial blood gas to assess the postintubation pH and PaCO_2 allows further ventilator titration.

CONCLUSION

This review provides a framework for clinicians to help identify and manage the primary physiologic dangers of the peri-intubation period. The “*HOp* killers”—hemodynamic instability, hypoxia, or pH (acidosis)—is a useful mnemonic and suggests several adjustments and techniques to achieve preinduction optimization of the unstable patient. The decision to intubate an unstable patient should be coupled with the recognition of the differences in the physiology of the unstable patient from the routine preoperative patient. Routine intubation

practices can provide insufficient sedation, paralysis, preoxygenation, or ultimately prove fatal. The patient's physiology should guide adjustments to the medications, tools, and techniques to optimize the chances for a successful intubation.

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Emergency Surgical Airway

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The airway management of unstable and critically ill patients has always been an essential skill within the emergency physician's scope of practice. The early act of inserting an artificial airway protects the lungs from aspiration in an obtunded patient, or prevents hypoxia and carbon dioxide retention in a patient who cannot spontaneously breathe. This has been shown to improve neurologic outcome when performed early during the initial phase of resuscitation, and emergency physicians are often the first clinicians to perform intubation and initiate mechanical ventilation.¹

While direct laryngoscopy is associated with a high rate of success with few adverse events when performed by personnel skilled in its use, there are a number of clinical scenarios and presentations in which direct or indirect laryngoscopic intubation is difficult or impossible. Disruption of the normal anatomy due to body habitus, medical and surgical disease, or facial and oral trauma can result in soft-tissue and bony structure distortion. Obstruction or lack of laryngeal visualization can be caused by copious amounts of blood or vomitus, facial edema, vocal cord swelling from prolonged or multiple intubation attempts, anaphylaxis, angioedema, and burns.

When an emergency physician is called upon to perform urgent airway management, the approach to airway management should be standardized and similar in all contexts. Whether in the field with an emergency medical services (EMS) agency or in the hospital, a clinician should recognize when to abort further attempts at intubation through direct visualization and proceed to alternative techniques for

establishing an artificial airway. As discussed in the preceding chapter, inability to identify the vocal cords should prompt the use of a “difficult airway” algorithm that includes the use of intubation adjuncts such as tracheal tube introducers, alternative intubation devices such as video laryngoscopes, flexible fiberoptic scopes, lighted stylets, retrograde approaches, or the placement of a laryngeal mask airway (LMA).

When intubation is not successful, especially after administration of neuromuscular blockade, and when adequate oxygenation or ventilation with the bag–valve–mask technique cannot be achieved, a “failed airway” has occurred. At this point, cricothyroidotomy is the emergency medicine surgical airway of choice.^{2,3} It should be noted that the terms cricothyroidotomy and cricothyrotomy are synonymous and may be used interchangeably.

Fortunately, the incidence of the “failed airway” in the emergency department (ED) setting is low. Depending on the patient population and the skill level of the clinician, airway management databases report the use of a surgical airway in 0.03% to 1.8% of patients who require definitive airway management.^{4–8} When it does occur, a “failed airway,” sometimes referred to as a “cannot intubate–cannot ventilate” situation, requires a surgical airway be placed immediately. Unfortunately, when required, the establishment of an emergency surgical airway is associated with a high rate of complications, up to 14% in some reviews.⁹

Despite newer equipment and modified approaches, there remain two traditional emergent surgical airway procedures:

surgical open cricothyroidotomy and needle cricothyroidotomy. Both approaches require a firm understanding of the involved anatomy for a successful procedure, and a familiarity with the potential limitations and complications of each technique. Preparedness is the key to success.

CONTRAINDICATIONS OF CRICOTHYROIDOTOMY

This procedure has limited contraindications. Cricothyroidotomy should not be done if oral or nasal intubation has not been attempted or if there is significant trauma to the area, such as fracture of the larynx or transection of the trachea.

The surgical approach is contraindicated in children younger than 10 to 14 years old due to the underdeveloped larynx; however, the exact age cutoff is not well established in the medical literature. The cricoid ring in children is the narrowest portion of the airway, much like a funnel, with the vocal cords being the widest space. This is generally the opposite in the adult. For this reason, needle cricothyroidotomy is the preferred airway in young children.

ANATOMY

The cricothyroid membrane is located between the thyroid and cricoid cartilages (Figure 3-1A). Both structures are usually easy to palpate in a patient with normal anatomy. However, localizing the key anatomical landmarks through a tactile approach may be more difficult in certain populations. In particular, there is evidence that in obese individuals, and in females more than males, misidentification of the cricothyroid membrane is common.¹⁰ Likewise, in the edematous intensive care unit (ICU) patient, the anatomy can be extremely difficult to palpate. By applying pressure over the area of the larynx for several seconds, however, the edema fluid will be dispersed and the anatomic landmarks may be appreciated. Blindly, the cricothyroid membrane can be found approximately one-third of the distance from the manubrium to the chin, in the midline, in patients with a normal habitus (Figure 3-1B). Of note, the potential use of ultrasound as a tool for localizing the cricothyroid membrane has not been validated, and this modality of imaging may be ill-suited for quick identification of the location where a surgical airway should be focused.¹⁰ This is because the density

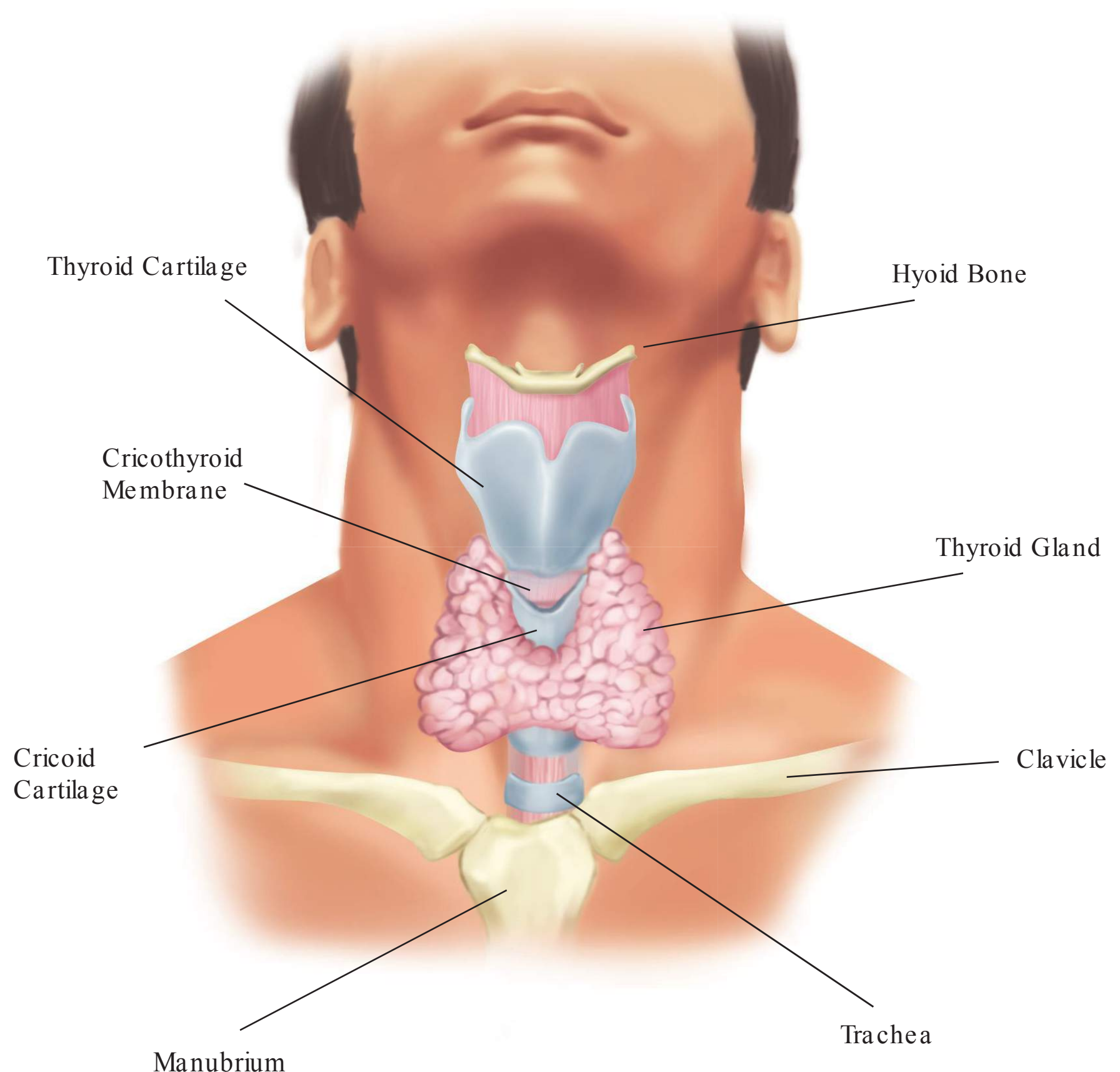


FIGURE 3-1 (A) Anatomy of the neck. (Reproduced with permission from Cline D, Ma, OJ, Tintinalli JE, et al: *Emergency Medicine: A Comprehensive Study Guide*, 5th ed. New York: McGraw-Hill Inc; 2000.)

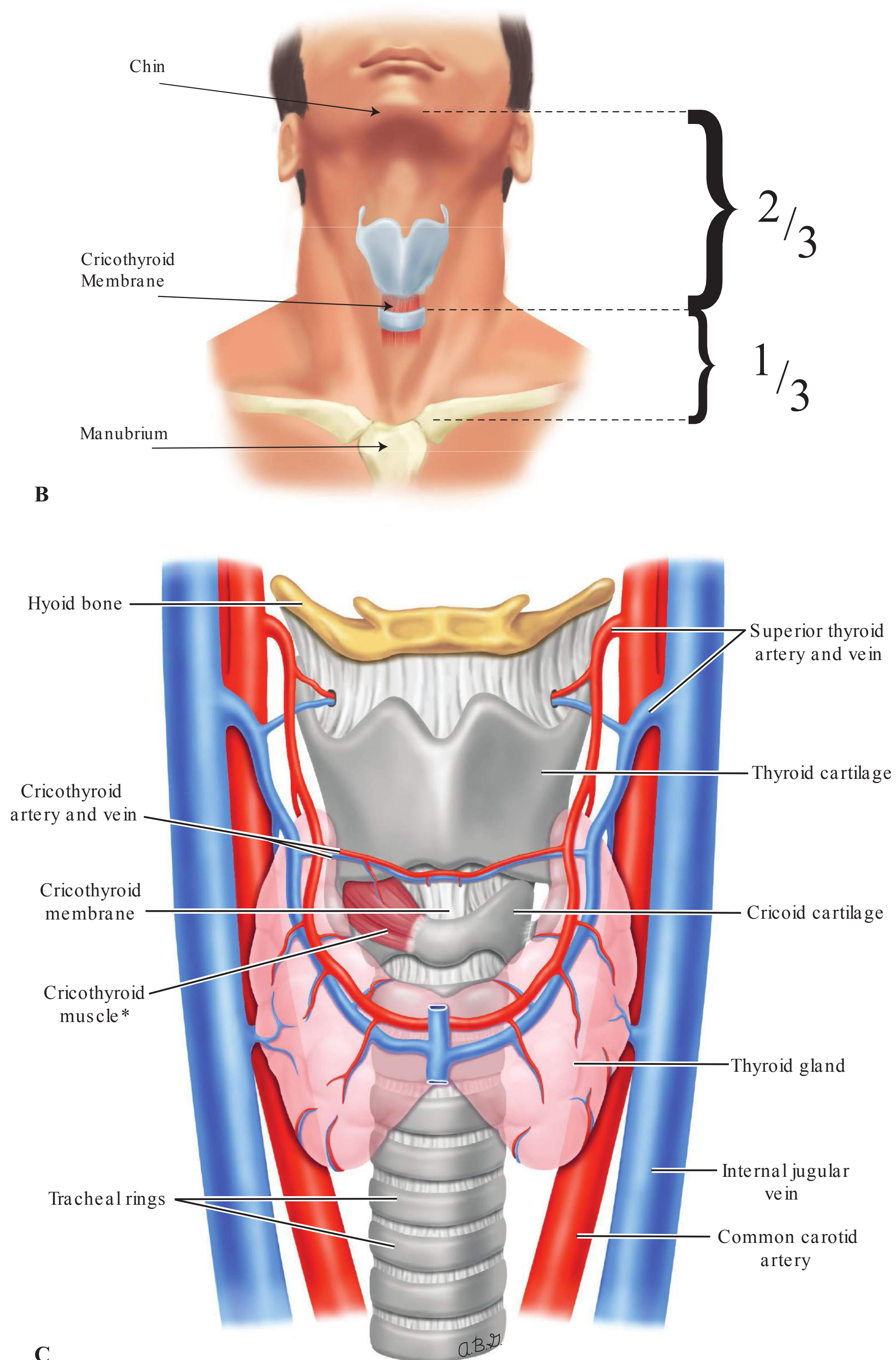


FIGURE 3-1 (Continued) (B) Location of the cricothyroid membrane. (Reproduced with permission from Cline D, Ma, OJ, Tintinalli JE, et al: *Emergency Medicine: A Comprehensive Study Guide*, 5th ed. New York: McGraw-Hill Inc; 2000.) **(C)** Anatomy of the cricothyroid membrane. *The cricothyroid muscle is bilateral and depicted on one side for illustrative purposes. Note the cricothyroid artery and vein. (Reproduced with permission from: Bair AE. *Emergency surgical cricothyrotomy (cricothyroidotomy)*. In: UpToDate, Post TW (Ed), UpToDate, Waltham, MA. (Accessed on August 3, 2016) Copyright © 2016 UpToDate, Inc. For more information visit www.uptodate.com.)

of cartilage in comparison to its neighboring anatomic neck structures does not provide the contrast in acoustic interfaces that make solid organs and bony structures easy to characterize with this technology.

The thyroid cartilage is the largest cartilage on the anterior neck. Inferior to the thyroid cartilage is the beginning of the cricothyroid membrane. The superior thyroid prominence, which is often very obvious and is commonly referred to as the “Adam’s apple,” is the most important landmark for cricothyroidotomy. The cricothyroid artery and vein, which are branches of the superior thyroid artery and vein, run closer to the superior border of the membrane at the inferior portion of the thyroid cartilage. These vessels anastomose in the middle of the membrane (Figure 3-1C). There are usually no vessels at the lower part of the membrane near the superior aspect of the cricoid cartilage; however, a small percentage of patients may have a “thyroid ima” artery that may pass over the inferior portion of the membrane.

SURGICAL CRICOTHYROIDOTOMY

In the adult patient, a surgical cricothyroidotomy is the preferred approach. A definitive airway is established with a cuffed tube in the trachea, and provides a means for adequate artificial oxygenation and ventilation, allowing the resuscitation to continue. The needle method should only be used as a temporizing method until an open cricothyroidotomy or a tracheostomy can be performed due to the ease of catheter dislodgement and bending. The less optimal ventilation with needle cricothyroidotomy can also cause hypercapnia, which may worsen acidosis.

Cricothyroidotomy, rather than tracheostomy, is the preferred initial surgical airway of choice for the failed airway patient. Emergent tracheostomy has a more severe set of complications, such as posterior tracheal laceration, esophageal perforation, and pneumothorax. It is also technically more challenging, even in the percutaneous approach. Tracheostomy, however, is a definitive airway and should be reserved for placement under well-controlled conditions.

Although cricothyroidotomy is an emergent procedure, sterile technique should be employed when possible. In every circumstance, gloves and a face shield with mask should be worn by the proceduralist. Suction should be available. Furthermore, time should be taken to position the patient in a supine position with the neck extended if no cervical injuries are suspected. The patient should remain on supplemental oxygen as long as it does not interfere with or alter the anatomic landmarks.

ICU beds are not generally suitable for any operation: the beds are wider than an operating room (OR) table or ED stretcher and the operator is further away from the patient and therefore must bend over considerably. If the procedure must be performed in an ICU bed, the patient should be moved as close to the side of the operator as possible. If time permits, prepare the neck using either povidone iodine or chlorhexidine solution. The appropriate equipment for the planned technique should be ready and available (Table 3-1).



TABLE 3-1: Equipment for Surgical Cricothyroidotomy

1. Povidone iodine or chlorhexidine gluconate solution
2. Personal protective equipment
3. Scalpel
4. A 6-mm ID endotracheal tube: tubes greater than 6 mm are extremely difficult to place through the cricothyroid membrane (or tracheostomy tube: size 4 or 6 cuffed)
5. Tape to secure the endotracheal tube in place (or tracheostomy tube)
6. Bag–valve–mask device or ventilator and an oxygen source

SURGICAL TECHNIQUE

One of the major problems with performing surgical and needle cricothyroidotomy is the lack of experience among most practitioners. Furthermore, even among those with experience, or who have practiced extensively under laboratory conditions, skills maintenance is difficult at best. There are simply too few opportunities to clinically utilize this important skill on a regular basis. A 5-year review at the Hennepin County ED found that cricothyroidotomy was performed in only 1% of intubations.¹¹

Given the complexity and importance of the skill set, other techniques and equipment have been developed. The Seldinger technique for percutaneous cricothyroidotomy has many advantages over open cricothyroidotomy. First and foremost is comfort. Although open cricothyroidotomy has traditionally been taught as the airway management maneuver of last resort, the large number of other procedures done percutaneously with Seldinger technique (such as central lines and some arterial lines and chest tubes) make this approach a logical choice for many practitioners. Commercial Seldinger cricothyroidotomy kits are available such as the Cook® Melker kit (Figure 3-2).

There are also good data to show that the Seldinger technique yields better outcomes when compared with open cricothyroidotomy. Schaumann et al. showed that not only



FIGURE 3-2 Cook®Melker Emergency Cricothyrotomy Catheter Tray. (Used with permission from Cook Medical Incorporated, Bloomington, Indiana.)



FIGURE 3-3 Cook® Cuffed Emergency Cricothyrotomy Catheter. (Used with permission from Cook Medical Incorporated, Bloomington, Indiana.)

did the Seldinger technique result in a shorter time to successful ventilation, but it resulted in fewer injuries as well.¹² It is also worth discussing the one unique piece of equipment for this procedure, a commercially available cuffed emergency cricothyroidotomy catheter (Figure 3-3) that looks similar to a tracheostomy tube but with a 5-mm diameter. Much like a tracheostomy tube, it comes with a dilator as well. One advantage of the Melker kit is that it can be used for both the Seldinger technique and the open technique, so that in the chaotic environment of the ED everything necessary is readily available.

If a commercial kit is not available, it is recommended that a kit be prepared ahead of time with all the necessary equipment to prevent delay. Keep in mind that the inner diameter of the tube should not exceed 6 mm. A 6.0 or 5.0 mm ID cuffed endotracheal tube (ETT) should be used if a cuffed emergency cricothyroidotomy catheter is not available. It is important to recognize, however, that it can be difficult to secure an ETT and that there is a risk of dislodgement or right main stem bronchus intubation. Familiarity with the type of equipment available, as well as its location, is essential for the success of this procedure.

CRICOTHYROIDOTOMY APPROACH

Open Technique

1. A right-handed practitioner should stand on the patient's right side, a left-handed practitioner to the left.
2. The cricoid ring is located by placing the index finger at the sternal notch and palpating cephalad until the first rigid structure is felt. This is the cricoid ring. Rolling the index finger one finger breath above should locate the "hollow" between the cricoid and thyroid cartilages. This is the cricothyroid membrane. One may also choose to locate the thyroid prominence at the midline of the thyroid cartilage, holding the cartilage in place with the nondominant hand, and rolling the index finger caudally by 1 or 2 cm until a small depression or "hollow" is felt. This is the cricothyroid membrane. This may be the technique of choice in an edematous patient or a patient with a larger neck. Attention should be paid to the vessels that run at the superior border of the membrane. In severe bleeding, or whenever a landmark cannot be located, a skin incision is made and a finger should be used to locate a key landmark.
3. The thumb and middle finger of the nondominant hand are then used to stabilize the two cartilages.
4. A vertical skin incision is then made in the midline of the region between the two cartilages. A #10 blade scalpel must be used for the incision and for the puncture of the cricothyroid membrane: It has a width that is greater than the width of the tip of a #6 ETT. A vertical skin incision is crucial because this incision can be extended if it is too high or too low, whereas a horizontal incision would require a new incision. Also, a vertical midline skin incision has less chance of cutting a vessel. The initial incision should go through the skin and subcutaneous tissues, but no deeper because of the risk of injuring the cricoid or thyroid cartilages or vascular structures.
5. With the scalpel blade now positioned horizontally, the cricothyroid membrane is perforated at the midline inferior portion of the membrane using a horizontal stabbing motion. The reason for the horizontal cut is to have a good horizontal aperture and to not cut the cricoid cartilage with the scalpel blade. The scalpel blade will slice the cricoid cartilage if inserted vertically. The blade should only enter the membrane by 1 cm in order to avoid complications.
6. Dilate the ostomy by inserting the back end of the scalpel handle through the cricothyroid membrane incision and rotate it 90° to widen the opening. The handle is slightly wider than the width of the blade.
7. Further dilate the ostomy with surgical tissue dilators, to remain in place to facilitate the following step in the procedure.
8. Finally, the ETT can be placed in the opening and the balloon inflated as in a traditional intubation. With the practitioner holding the ETT in place, the tube can be connected to a bag-valve-mask, and tube placement should be confirmed as with a traditional intubation (auscultation, color capnometry, esophageal detector, etc.).
9. The tube should be secured with a ribbon or adhesive tape.
10. As always, a portable chest x-ray should be obtained to ensure proper placement of the tube relative to the carina and to check for pneumothorax.

Holmes et al. reported a rapid four-step modified version of this open surgical technique that was found to be easier and quicker (performed in one third the time) when compared with the aforementioned open technique.¹³ This procedure forgoes the blunt dissection recommended in of the traditional technique after the initial vertical incision, and suggests eliminating the additional step of fixed ostomy dilatation during introduction of the tracheal tube.

Open Bougie Technique

In another variation of the open technique, Hill et al. found that insertion of a tracheal tube directly through the incision was challenging and modified the technique by placing a gum elastic bougie through a horizontal incision, then advancing the tracheal tube over the bougie.¹⁴

1. Arrange at the bedside a No. 10 or 20 blade scalpel, a tracheal hook, a gum elastic bougie ETT introducer, and a 6–0 endotracheal tube.
2. Identify the cricothyroid membrane through palpation, and then stabilize the larynx with the thumb and middle finger before making a transverse stabbing incision with the scalpel into the skin overlying the cricothyroid membrane.
3. Apply cephalad traction to the superior portion of the skin incision with the tracheal hook to retract the cartilage and expose the airway lumen.
4. Introduce the bougie through the incision site and into the lumen of the trachea.
5. With the bougie still in situ, place the ETT over the superior end of the bougie and thread it downward and into the trachea.
6. Remove the bougie, secure the tube as described in the open technique, and confirm appropriate placement with imaging.

More recently, a similar modified version of the original bougie technique has been proposed that involves only three steps: incision, bougie placement, and ETT placement over the bougie.¹⁵ This three-step method was shown to be superior to the traditional surgical approach in terms of procedure time in a simulation scenario, even when performed by personnel who were already experienced in the latter technique. It has also been suggested as the optimal cricothyrotomy approach for use in austere environments because it can be easily improvised with common medical equipment, and has a high success rate and minimal complications when performed by both experienced and novice personnel.¹⁶

Seldinger Technique

The procedure here is based on the Cook Melker kit.

1. Open the kit and insert the dilator with wire into the airway catheter (there are two dilators in the kit: one with a hole for the guide wire and one for the open technique that is blunted).

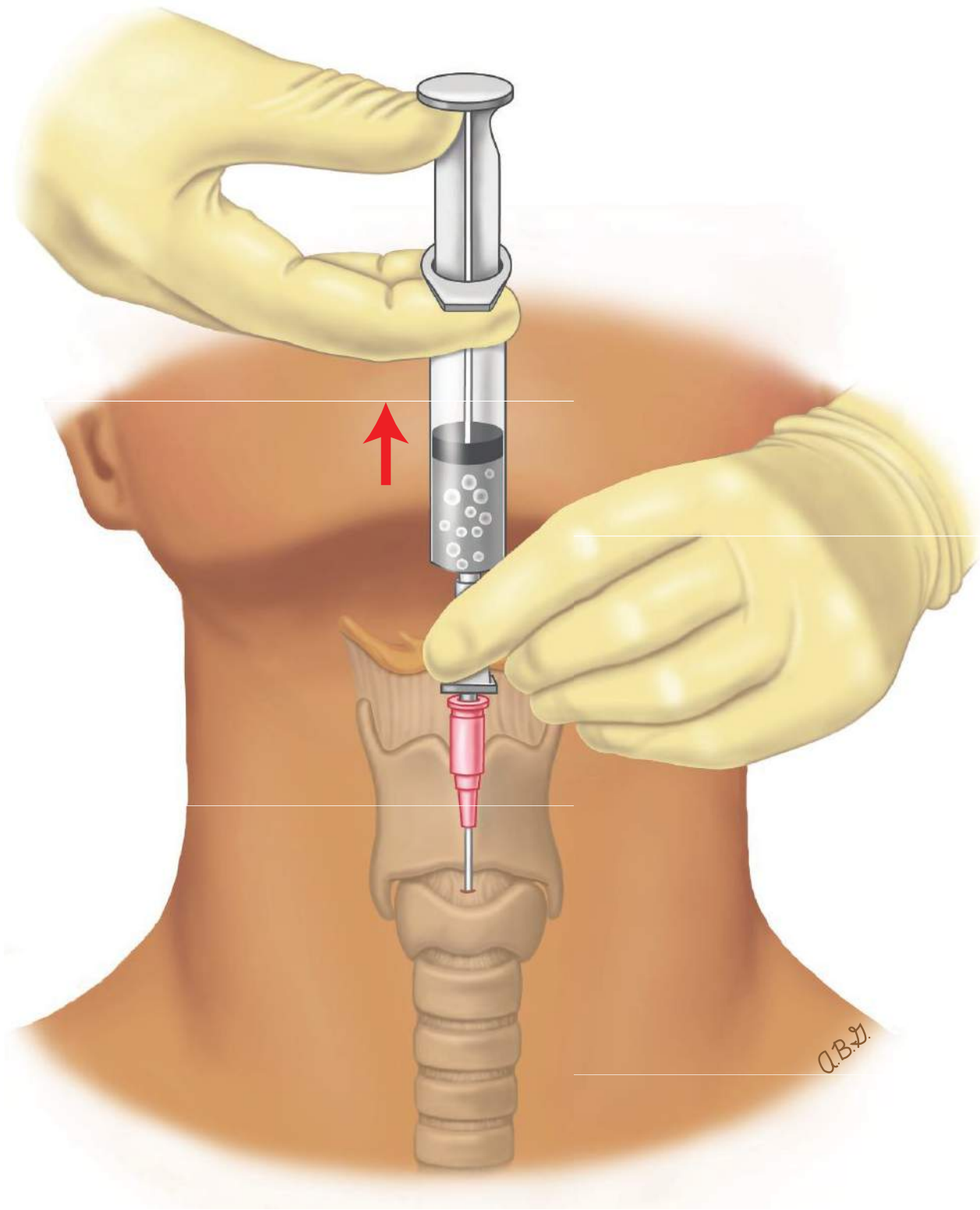


FIGURE 3-4 Syringe with “air bubble.” (Reproduced with permission from: Bair AE. *Emergency surgical cricothyrotomy (cricothyroidotomy)*. In: UpToDate, Post TW (Ed), UpToDate, Waltham, MA. (Accessed on August 3, 2016) Copyright © 2016 UpToDate, Inc. For more information visit www.uptodate.com.)

2. The cricothyroid membrane is located in the same manner as with the open surgical technique.
3. Attach the needle with the sheath to the syringe and fill the syringe with a small amount of water or saline. Insert the needle into the cricothyroid membrane. With the tip of the needle pointing to the feet in a 45–50° angle, gently puncture the membrane until bubbles are apparent in the syringe. This will confirm you are in the trachea. Use slow, gentle pressure so as not to damage the posterior wall of the trachea.
4. As soon as there is a “bubble” of air in the syringe (signaling entrance into the lumen of the larynx; Figure 3-4), the sheath is advanced over the needle and into the larynx, still at 45°. As with advancing an ETT via a surgical cricothyroidotomy, overzealous posterior advancement of the sheath may cause the sheath to get stuck on the cricoid cartilage posteriorly. In this case, the syringe with sheath should be withdrawn slightly and readvanced, taking care not to displace the sheath posteriorly.
5. Once placed, the needle can be removed, leaving the sheath in place in the larynx/trachea. The wire should be advanced through the sheath (Figure 3-5). The plastic sheath is then removed, leaving only the wire in place.

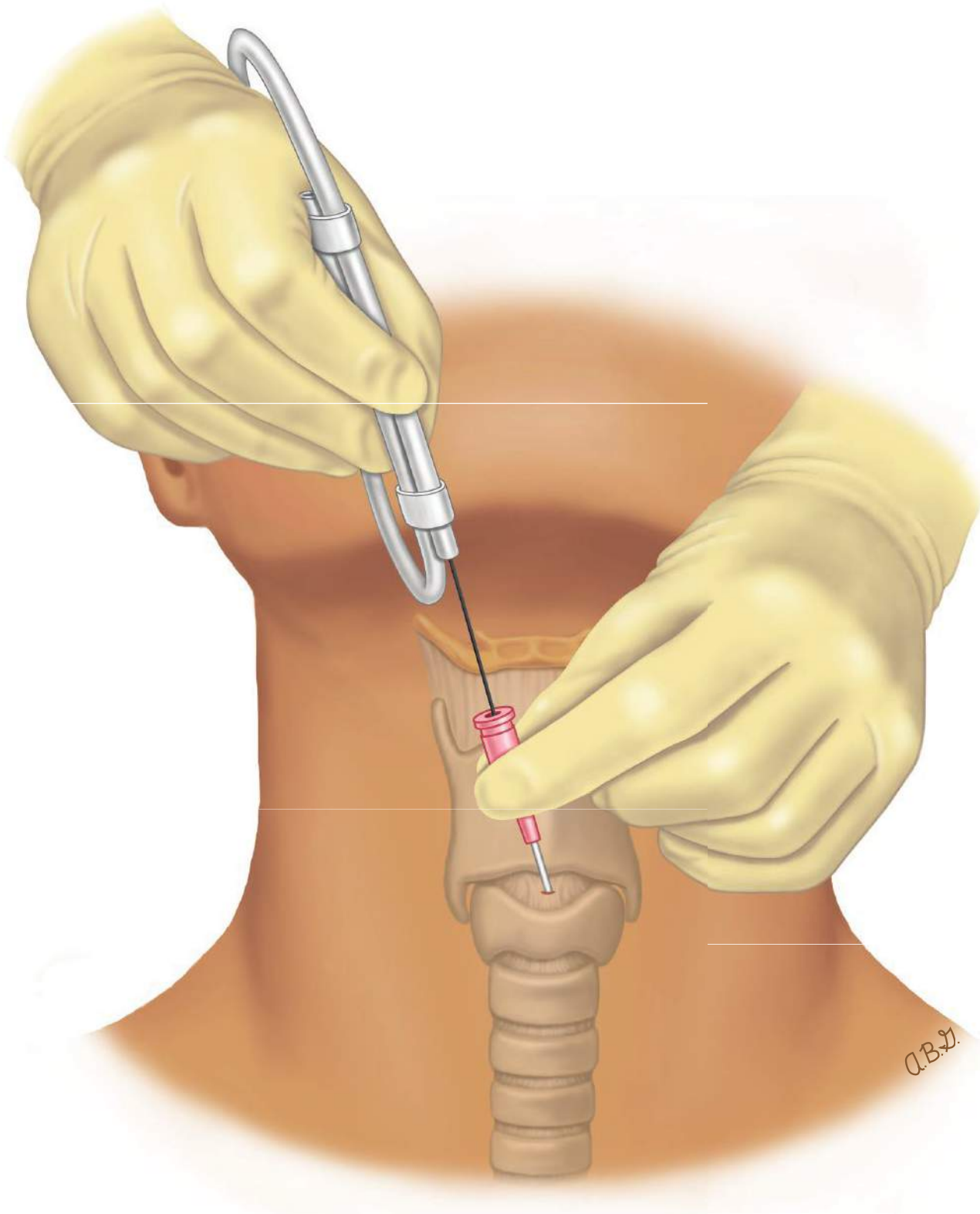


FIGURE 3-5 Place the guide wire through the catheter into the trachea. (Reproduced with permission from: Bair AE. *Emergency surgical cricothyrotomy (cricothyroidotomy)*. In: UpToDate, Post TW (Ed), UpToDate, Waltham, MA. (Accessed on August 3, 2016) Copyright © 2016 UpToDate, Inc. For more information visit www.uptodate.com.)

6. With the provided 15-blade scalpel, a 0.5-cm vertical skin incision should be made on both sides of the wire (taking care not to cut the wire). Remember that the catheter size is 0.5 cm, so a slightly larger incision will be necessary.
7. Insert the external end of the wire into the dilator, which was already placed into the cricothyroidotomy catheter. Advance them as a unit, following the curvature of the dilator, through the subcutaneous tissue and into the trachea. A twisting motion may be required so as not to bend the wire. Advance until the cricothyroidotomy catheter is flush against the skin (Figure 3-6). Once in place, the dilator is removed and the cuff inflated.
8. Secure the cricothyroidotomy catheter with the provided wrap. Confirm placement as discussed in the section “Surgical Technique.”

“Hybrid” Technique

Recognizing that the open and Seldinger-based percutaneous approaches need not be mutually exclusive, Kanji et al. have suggested that aspects of each technique can be used to create an “incision first” strategy that begins with a deep vertical incision as is used in the open surgical approach, followed by the introduction of the percutaneous needle and guide wire as described in the Seldinger technique.¹⁷ According to the

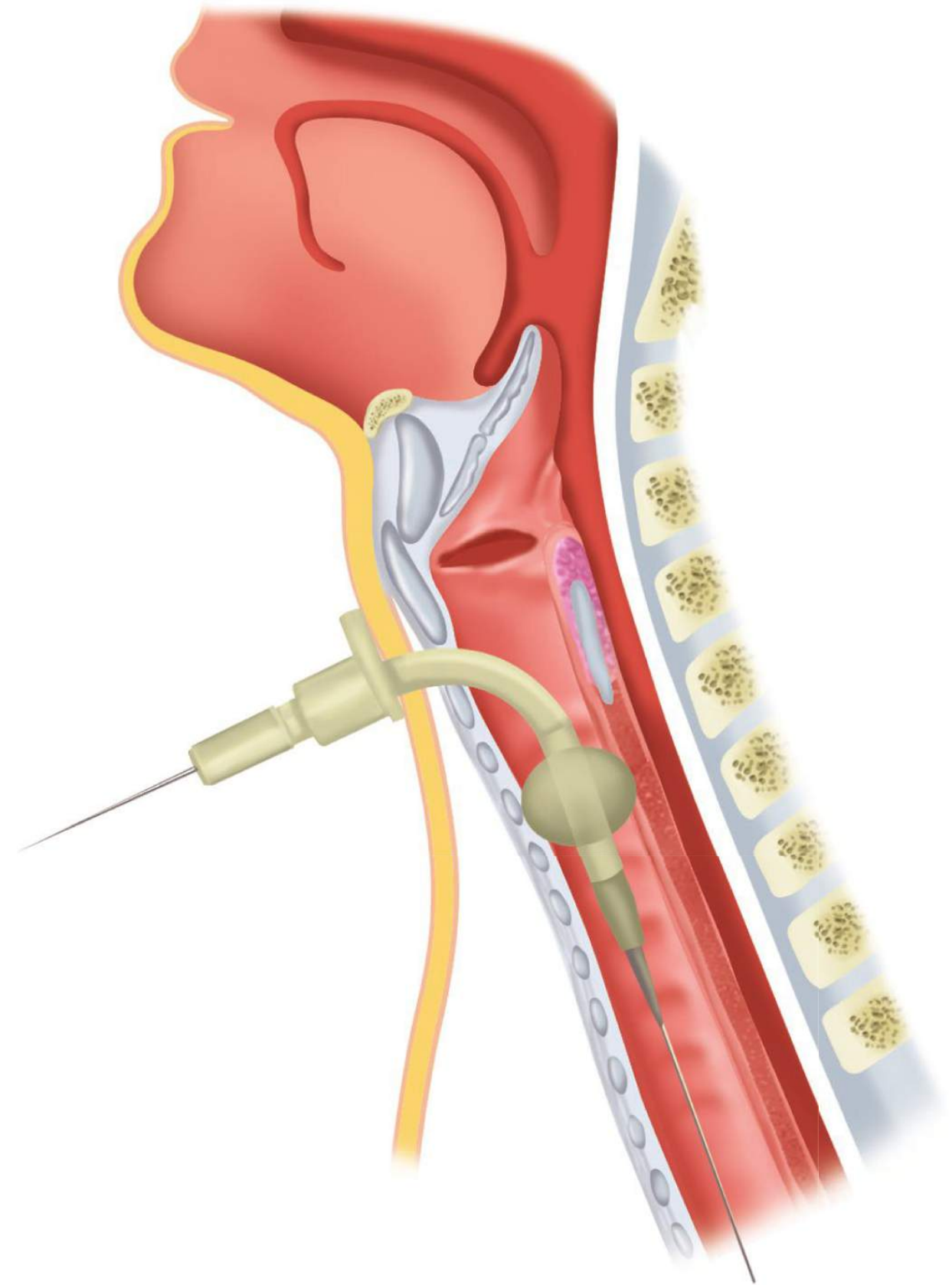


FIGURE 3-6 Cook®Cricothyrotomy Catheter with dilator and wire seen from a cross-sectional view. (Used with permission from Cook Medical Incorporated, Bloomington, Indiana.)

authors, making an initial open incision facilitates identification of the relevant anatomic structures and the optimal site for needle introduction. It can also prevent catheter and guide wires from deformation at the tougher surface of the epidermis by exposing the more pliable subcutaneous tissues. Using a swine trachea model, the study found that the hybrid “incision first” technique yielded both a higher success rate and quicker completion than the traditional percutaneous approach.

NEEDLE CRICOTHYROIDOTOMY

Needle cricothyroidotomy is the preferred emergency surgical airway technique in patients under the age of 10 to 14 years. This is because larger endotracheal or tracheostomy tubes placed through the cricothyroid membrane have a high complication rate in this age group, as previously discussed.¹⁸ Ventilation may be achieved, poorly, for approximately 20 to 30 minutes in a patient with normal lungs, which makes this procedure an inappropriate choice in an ICU patient. Furthermore, the airway established by a needle cricothyroidotomy is only a temporary measure. This measure will, however, provide an additional 30 minutes or so until a more definite airway can be established. Note that, even if placed correctly, there will be great resistance to ventilatory airflow because of the small lumen of the 12- or 14-gauge catheter.



TABLE 3-2: Equipment for Needle Cricothyroidotomy

1. Povidone iodine or chlorhexidine gluconate solution
2. Personal protective equipment
3. A 14- or 12-gauge sheathed needle catheter: 12 gauge is best
4. A 3-mL syringe
5. Adapter from the end of a 7-mm ID endotracheal tube
6. Wall oxygen source

See Table 3-2 for the needle cricothyroidotomy equipment.

Needle Cricothyroidotomy Technique

1. The cricothyroid membrane is located in the same manner and, as with a surgical cricothyroidotomy, the thumb and middle finger of the nondominant hand are used to stabilize the two cartilages.
2. A sheathed 14- or 12-gauge needle with a syringe attached is placed over the location of the cricothyroid membrane at 90° to the skin. Adding water or saline will create a “bubble” once air is aspirated from the trachea. If no water is added, a “gush” of air into the syringe will confirm tracheal placement.
3. Once the needle is in the trachea, the needle should be angled 45° caudally. The sheath is then advanced and the needle is removed. As with advancing an ETT via a surgical cricothyroidotomy, overzealous posterior advancement of the sheath may cause the sheath to get stuck on the cricoid cartilage posteriorly.
4. The adapter from the end of a 3.0-mm ID ETT can be attached to the end of the catheter, and an Ambu bag or ventilator attached to the adapter. Alternately, a 3-mL syringe (without plunger) can be attached to the catheter to “step up” the size of the connection. An adaptor from the end of a 7.0-mm ID ETT can then be attached to the syringe barrel and the Ambu bag or ventilator can be attached to the adapter.
5. The catheter must be held in place manually by a provider until a proper tracheostomy is performed (which should be immediately). Because of the pressure delivered through the small lumen, the sheath cannot be secured with tape or any other device; it must be manually held in place.
6. While preparations are being made for an emergent tracheostomy, a chest x-ray should be obtained. Massive subcutaneous air could imply misplacement of the catheter into the subcutaneous tissues of the neck.

CRICOTHYROIDOTOMY CONVERSION

The question frequently arises as to how long to leave a cricothyroidotomy tube in place in the larynx and at what point it should be converted to a formal tracheostomy. A tube left in place in the narrow space between the two cartilages can erode either one or both of these cartilages and bacterial chondritis

may occur. This can lead to scarring and subsequent laryngeal or tracheal stenosis with loss of laryngeal function. As a rule of thumb, if the airway will be needed for more than 2 days, the cricothyroidotomy should be changed to a tracheostomy; otherwise, the cricothyroidotomy tube may be left in place. For example, in a patient who needs a surgical airway because of anaphylactic or angioedema-related airway swelling, the condition may resolve in a matter of hours, allowing for simple decannulation. If the cricothyroidotomy is to be converted to a tracheostomy, it should be done in a controlled setting with proper instruments and lighting by an appropriate practitioner, whether a surgeon in an OR or an intensivist in the ICU.

COMPLICATIONS

Needle cricothyroidotomy and surgical cricothyroidotomy (whether done in an open manner or with the Seldinger technique) share some common complications.

Bleeding may occur, especially if the thyroid ima artery is injured. This artery is present in 4% to 10% of individuals, arises from the aorta or brachiocephalic artery, stays in the midline, and may travel cephalad as high as the thyroid cartilage.¹⁹ Once an injury to this artery is recognized, the patient should be taken to the OR to have the artery controlled by ligation. Most bleeding, however, is from small branches of the anterior jugular veins. These veins usually have very high venous pressures due to the high airway pressure in many ventilated ICU patients, or in the patient trying to breathe against an obstructed airway (Valsalva). Once the airway is obtained, the intravenous pressure drops and the bleeding usually stops.

Pneumothorax from placement of a surgical airway is usually due to barotrauma from forceful ventilation and high airway pressures toward the end of the procedure. Once the airway is secure, a pneumothorax should be treated just as one that arose from any other condition, with tube thoracostomy.

In an obese or edematous neck or in one with altered anatomy from a tumor or prior surgery, it is possible to **misplace** the cricothyroidotomy catheter, ETT, or needle anterior to the larynx and trachea and into the mediastinum. Ventilation in this setting is obviously not possible. Manifestations of an incorrectly positioned tube are high airway pressures, absent breath sounds, and massive subcutaneous emphysema. When a malpositioned tube is recognized, the tube should be removed and a second attempt should be made.

Laceration or perforation of the structures of the neck, such as the trachea, esophagus, or recurrent laryngeal nerves, is extremely rare and is usually due to inadequate knowledge of the anatomy of the neck. Laceration of the thyroid ima artery, when present, may be unavoidable because it cannot be visualized through the incision.

Late airway complications may occur in up to 52% of cases. These complications include voice changes and laryngeal and/or tracheal stenosis.²⁰⁻²³ They usually manifest after the course of the critical illness and are not emergent conditions, although they require evaluation and treatment as they may be debilitating for the patient.

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Mechanical Ventilation

David A. Farcy • Nirav G. Shah • Paul L. Petersen • Peter M.C. DeBlieux

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Mechanical ventilation (MV) is an essential tool for critically ill patients. While emergency physicians are well known for their expertise in emergent airway management, securing the airway is only a fraction of their role. Ventilator management is a crucial facet of emergency medicine, because if it is not applied correctly, it can worsen the clinical course and increase morbidity and mortality.¹ In the past two decades, our understanding of ventilator-induced lung injury (VILI) has resulted in lowering tidal volumes, minimizing barotrauma, and safely using positive end-expiratory pressure (PEEP) to reduce atelectrauma. In addition, we have realized the importance of mitigating patient-ventilator dyssynchrony in order to eliminate biotrauma. Given the current crisis of intensive care unit (ICU) overcrowding and increased critical care volume, critically ill patients have increased lengths of stay in the emergency department (ED) and, at times, are boarded for several hours or even days until a bed is available in the ICU.^{2,3} The emergency physician must understand the intricacies of MV for heterogeneous patient populations with dynamic pathologies: No “single setting fits all.” Both patient care and outcomes will improve with special consideration of each patient’s needs.

INDICATIONS FOR MECHANICAL VENTILATION

Indications for intubation and institution of MV fall under three basic categories: respiratory failure, airway protection, and anticipation of clinical deterioration. The most common

indication for MV is either hypoxic or hypercapnic respiratory failure. These patients frequently have ventilation/perfusion mismatch (a decrease in ventilation or an increase in perfusion to a normally ventilated lung), hypoventilation, shunt, or a decreased ability to manage the work of breathing. These can lead to hypoxemia, hypercapnia, or both. Hypoxemia is often defined as a P_{O_2} less than 60 mm Hg and hypercapnia is often defined as a P_{CO_2} greater than 50 mm Hg.

Since hypercapnia is a component of hypoventilation directly and indirectly results in elevation of CO_2 , an exact number is less important than the clinical picture. For example, in certain populations, such as patients with COPD who chronically retain CO_2 , a higher baseline P_{CO_2} of 45 to 55 mm Hg can be well tolerated. However, an acute rise in CO_2 from the patient’s baseline can cause lethargy, sleepiness, confusion, and altered mental status. In these hypercapnic patients, the primary action of MV is the promotion of appropriate alveolar ventilation with an end goal of enhanced CO_2 clearance.

In the ED, acute intoxication, altered mental status, and massive upper gastrointestinal hemorrhage are commonly seen and are another indication for MV in order to protect the airway from aspiration that could cause significant morbidity and even mortality.

Last, the predicted clinical course will often dictate securing an airway to either facilitate workup, offer definitive treatment, or to stabilize a clinical situation that may be likely to progress to clinical decompensation. For instance, a patient who is

hemodynamically unstable, in need of an endoscopic procedure (either bronchoscopy or endoscopy), or with the potential to clinically decompensate rapidly should be intubated prior to leaving the ED.

While there are no absolute contraindications for MV, there are potentially significant adverse effects of both intubation and MV. For example, arterial hypotension, secondary to the medications used for intubation and/or auto-PEEP, is a known complication in the peri-intubation period and is associated with increased morbidity and mortality (see chapter 2). In addition, traumatic injury from the intubation itself and VILI in the form of barotrauma or volutrauma can increase morbidity. Further, the placement of an endotracheal tube (ETT) removes the protective functions of the upper airway: gas heating, gas humidification, air filtration, and protection from aspiration. The ETT decreases effectiveness of removing secretions by expelling them through coughing and results in a loss of speech and an increase in airway resistance. These effects of intubation and mechanical ventilation are seen frequently and should be considered prior to placing a patient on the ventilator.

BASIC PHYSIOLOGY

Appreciation of the fundamental concepts of respiration is essential for the care of a mechanically ventilated patient. The most important parameter to understand and become familiar with is minute ventilation, which is the product of tidal volume and the respiratory rate (Table 4-1). Normal minute ventilation is 5 to 7 L/min. However, not all of the tidal volume reaches the alveoli because of dead space. Dead space can be anatomic or pathologic. Anatomic dead space exists because gas exchange does not occur in the trachea, larger airways, or ventilator tubing. It is usually estimated as 150 mL or 2.2 mL/kg lean body weight.⁴ Pathologic dead space exists due to ventilation/perfusion (V/Q) mismatch, shunting, and decreased diffusion across a diseased capillary-alveolar interface. Lower minute ventilation will result in hypoventilation with a resulting increase in P_{CO_2} . This will directly affect the acid-base balance, resulting in an acidemia and may also lead to hypoxemia. In contrast, supranormal minute ventilation will lead to a decrease of P_{CO_2} , resulting in an alkalemia and symptoms of numbness, tingling, and lightheadedness. This underscores the importance of considering minute ventilation, which should be adjusted based on the clinical picture rather than a particular number, when ordering the initial ventilator settings.



TABLE 4-1: Common Formulas for Respiratory Physiology

Minute ventilation (V_E) = tidal volume (V_T) \times respiratory rate (RR)

Compliance (C) = $\Delta V / \Delta P$ or tidal volume / $P_{plat} - PEEP$

Predicted body weight (PBW)

Male = $50 + (2.3 \times [\text{height in inches} - 60])$

Female = $45.5 + (2.3 \times [\text{height in inches} - 60])$

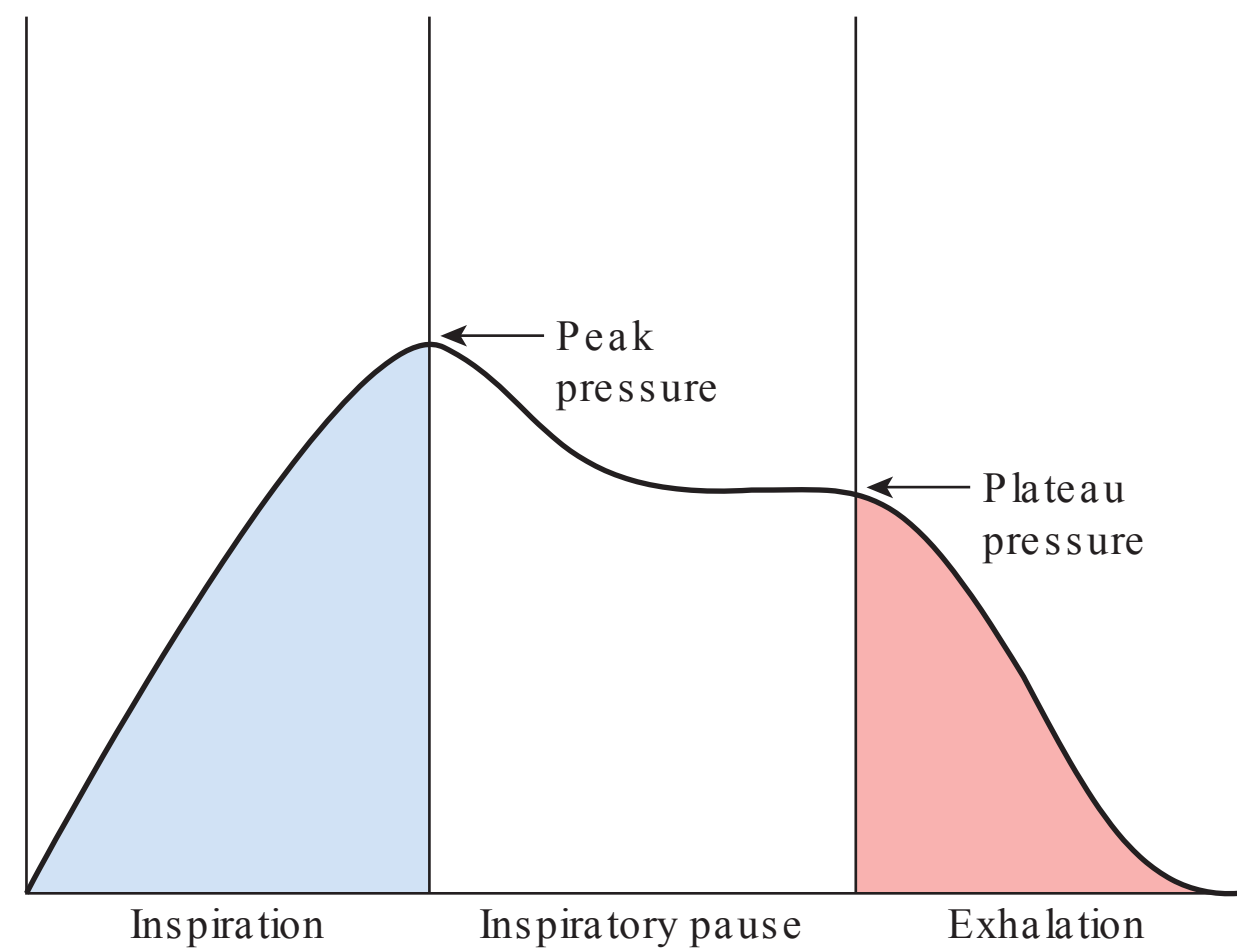


FIGURE 4-1 Peak inspiratory and plateau pressure.

Compliance is a measure of the distensibility of the respiratory system. It is the inverse relationship between the change in volume (ΔV) accommodated per change in pressure (ΔP) (Table 4-1). Total compliance is a sum of the chest wall and lung compliances. Decreased compliance is seen in pulmonary/chest wall edema, pulmonary fibrosis, pneumonia, sarcoidosis, or increased intra-abdominal pressure. Increased compliance is seen in emphysema. Ventilator settings should be tailored in patients with abnormal compliance to optimize oxygenation and minimize the risk of VILI.

Airway resistance is the amount of pressure needed to deliver a given amount of airflow. It is mainly a function of the larger airways because velocity is inversely proportional to area and the smaller airways exist in parallel, rather than in series. These concepts affect two important variables of MV: peak inspiratory pressure (PIP) and plateau pressure (P_{plat}). Both are easily measured on the ventilator (Figure 4-1) and should be reported when discussing patients who are on a volume-controlled mode of MV.

The PIP is a dynamic pressure measurement during maximal end inspiration. Both airway resistance and lung compliance influence it. This pressure only reflects upper airway pressure and not the transalveolar pressure, or pressure across an alveolus. When an end-inspiratory pause is applied after maximal inflation, the airway pressure decreases and then reaches a steady state. This resulting value is the P_{plat} . Elasticity, or the pressure needed to expand the lungs and chest wall, is often associated with P_{plat} , but this pressure measurement is a function of the total compliance and reflects the mean airway pressure of all of the airways. P_{plat} , not PIP, is the force the lung experiences at the alveoli, and as such has been used as a marker to estimate transalveolar pressure (Figure 4-2). A helpful equation to better understand this concept is: Airway pressure = Flow \times Resistance + Alveolar pressure. Flow is zero when an inspiratory hold is performed, thus the measured airway pressure is an estimate for alveolar pressure.

Elevated plateau pressures greater than 30 cm H_2O , according to a study conducted by the Acute Respiratory Distress Syndrome (ARDS) Network, has shown a significant

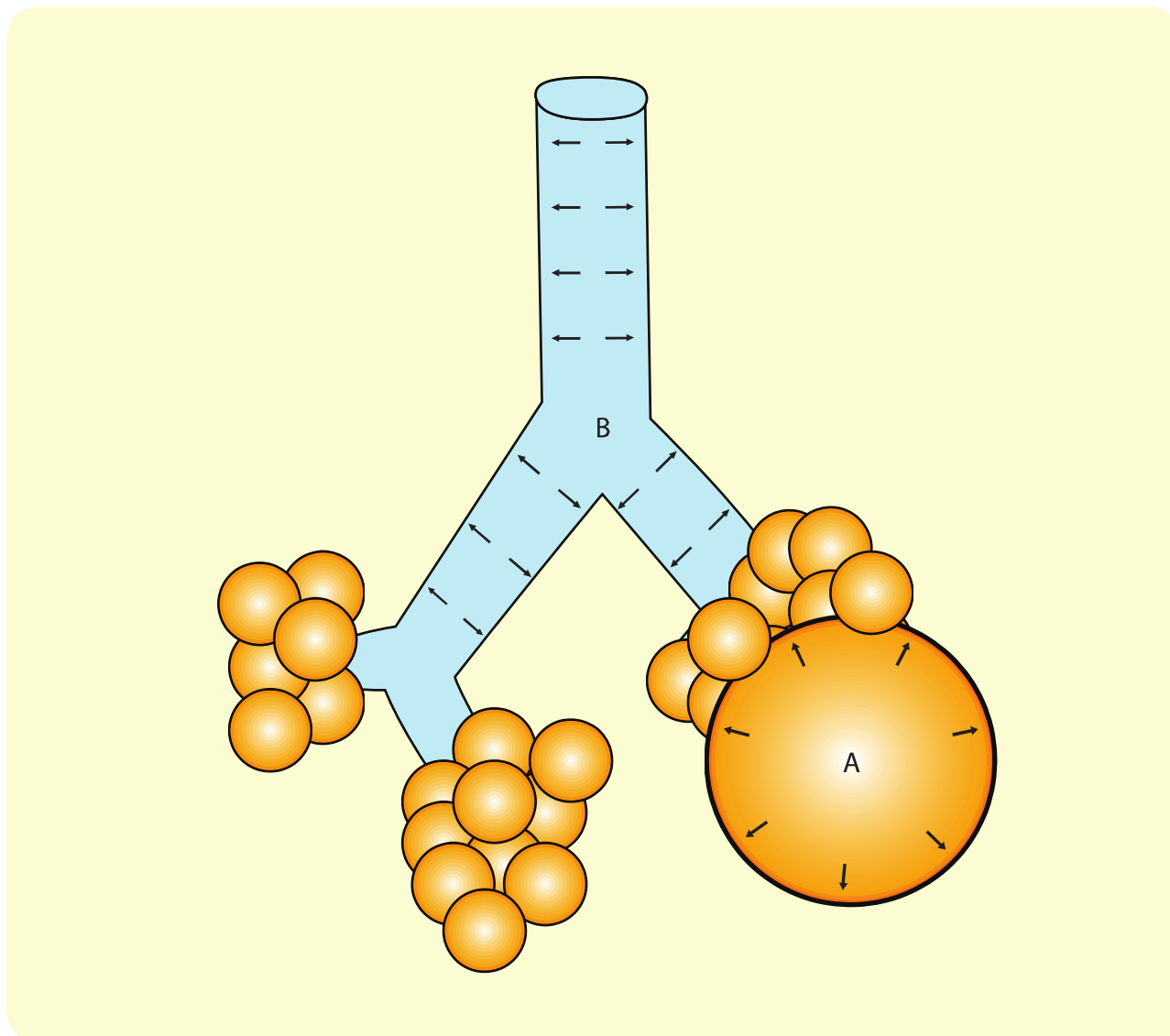


FIGURE 4-2 **A.** P_{plat} (plateau pressure): a trans-surrogate for alveolar pressure. **B.** PIP (peak inspiratory pressure): a trans-surrogate for bronchiolar pressure.

increase in mortality (further discussed later).¹ Consideration of the P_{plat} leads to significant changes in clinical decision making.

Following the PIP, P_{plat} becomes instrumental during MV. Careful attention and proper alarm settings will alert the astute physician to potential problems. Anticipation and direct action of abnormal pressures can identify the likely cause of the problem. First, one looks at the PIP. A sudden unexpected decrease in PIP is due to an air leak, inadvertent change of the ventilator settings, or self-extubation. The upper limit of normal for PIP is 35 cm H₂O. When the PIP is increased, the physician should reflexively check the P_{plat} . A normal P_{plat} indicates increased airway resistance due to either bronchospasm or an obstruction reducing the ETT diameter. Biting, kinking, or twisting of the ETT can cause these obstructions. They may also be caused by blood, foreign bodies such as mucus plugs, and aspiration. An elevated P_{plat} indicates an increase in the tidal volume or a decrease in lung and chest wall compliance which can be due to pneumothorax, gas trapping (also known as auto-PEEP or intrinsic PEEP), atelectasis, or any of the previously mentioned medical conditions associated with decreased compliance (see troubleshooting mechanical ventilation section and table 4-2).

Ventilator waveforms can assist a clinician in making a diagnosis. We should routinely be looking at the pressure, flow, and volume waveforms on the ventilator display. The pressure waveform can help identify airway obstruction, dyssynchrony, active exhalation against a closed ventilator circuit, triggering effort, obstruction, as well as bronchodilator response. The flow waveform will help the clinician identify the type of breath being delivered, auto-PEEP, dyssynchrony, triggering effort, and airway obstruction.

The three ways to identify auto-PEEP on the flow waveform are: 1. if the expiratory flow does not come back to baseline prior to initiation of the next breath, 2. if the area under the curve of the inspiratory arm of the waveform does not approximate the area under the curve of the expiratory arm, and 3. if there is double-triggering of the ventilator resulting in two breaths being delivered back to back. The volume waveform is often ignored but can yield useful information including leaks in the circuit, dyssynchrony, and how much tidal volume is actually being delivered. Simply glancing at the ventilator display for a few seconds can help the clinician identify issues with how MV is being delivered to a patient.

RISKS OF MECHANICAL VENTILATION

The primary goal of MV is oxygenation and ventilation; of equal importance is the avoidance of VILI to the already compromised lung tissue. The key factors are mainly alveolar damage from shear and strain stresses.

Barotrauma and volutrauma result from strain on the alveoli in the form of overdistention related to pressure or excess tidal volume and are important factors contributing to acute lung injury leading to alveolar fracture and rupture. Additional effects of alveolar rupture can stem from the liberation of inspired air into the various spaces around the lung: pleural cavity (pneumothorax), mediastinum (pneumomediastinum), or simply the pulmonary parenchyma (pulmonary interstitial emphysema). Alveolar fracture and rupture is often referred to as microbarotrauma, whereas macrobarotrauma refers to visible air in spaces around the lung.

Atelectrauma occurs at low lung volumes with increased respiratory rates to maintain minute ventilation. The repetitive collapsing and rapid inflation of alveoli produces a shear stress that can tear the thin, fragile alveolar–capillary interface. Creation of hyaline membranes and epithelial sloughing results from this rapid opening of alveoli. In addition, the surfactant function is compromised and areas of regional hypoxia are created.⁵

Biotrauma is the multiorgan injury caused by the body's immune responses to these injuries. Volutrauma and atelectrauma cause a direct or indirect activation of the cell-signal pathways in the epithelial and endothelial cells, causing an over production of the inflammatory mediators and cascade response (cytokines, neutrophils, and production of the endothelium and arachidonic acid pathways) that infiltrate the bloodstream through the compromised alveolar–capillary interface. This produces both local lung injury and potential distant multiorgan injury.^{5–7}

The severity of preventilation abnormalities can influence the development of VILI and its effects on gas exchange.⁸ In one study, repetitive collapse and reopening of terminal units did not injure healthy lungs, although it did decrease compliance and alter gas exchange.⁹ However, other studies illustrate the increased susceptibility of diseased lungs to the adverse effects of MV.

Lung Protective Strategies

Based on animal data, $P_{\text{plat}} > 35 \text{ cm H}_2\text{O}$ has been associated with alveolar injury. This has led to the concept and strategy of “lung-protective ventilation.”¹⁰ In addition, the ARDS Network Trial conducted, a landmark multi-center, randomized study on ARDS patients requiring MV illustrating that a lung-protective strategy with reduced tidal volumes of 6 mL/kg predicted body weight (PBW; see Table 4-1) showed a significant decrease of days on a ventilator and a decrease in mortality when P_{plat} was less than 30 cm H₂O versus the non-controlled group, which received traditional tidal volumes of 12–15 mL/kg PBW.¹ Tidal volumes of 12 to 15 mL/kg PBW were shown to be detrimental to the general population. A recently published meta-analysis from 2012 concluded that patients without ARDS also benefited from lung-protective ventilation with lower tidal volume, resulting in improved clinical outcomes. We recommend using tidal volumes between 6 to 8 mL/kg PBW in non-ARDS patients and 4 to 6 mL/kg for patients with ARDS (Figure 4-3).

Using lower tidal volumes can result in reduced minute ventilation, which should be compensated for by using higher respiratory rates and allowing permissive hypercapnia. Permissive hypercapnia is the acceptance of hypoventilation and resultant CO₂ retention caused by reduced tidal volumes selected to prevent alveolar injury. The retention and breakdown of CO₂ then leads to acidemia. A pH as low as 7.2 has been shown to be well tolerated; thus, the goal should not be to obtain a “perfect” arterial blood gas at the risk of causing VILI.¹¹

MODES OF MECHANICAL VENTILATION

After the airway has been secured, physicians must decide on the mode, target, and variable settings in their orders. This discussion will begin with the four common basic modes of ventilation that most ventilators can deliver: assist/control (A/C), intermittent or synchronized mandatory ventilation (IMV), pressure support ventilation (PSV), and continuous positive airway pressure (CPAP; see following section for discussion). Figure 4-4 provides a graphic representation of how the patient and ventilator interact with the different modes of ventilation. It is important to learn basic ventilator terminology. Control or target refers to how the ventilator knows how much flow to deliver; cycling is defined as the mechanism by which the phase of the breath switches from inspiration to expiration; and triggering is what causes the ventilator to cycle to inspiration from expiration. In addition, when looking at the ventilator graphics, scalars are waveforms that plot pressure, flow, or volume versus time and loops are waveforms that plot pressure or flow against volume. A large amount of information regarding patient-ventilator synchrony can be gathered from a simple glance at the waveforms and scalars after a patient has been placed on MV.

A/C is a combination of two types of MV. Assist mode allows the patient to spontaneously initiate a fully assisted,

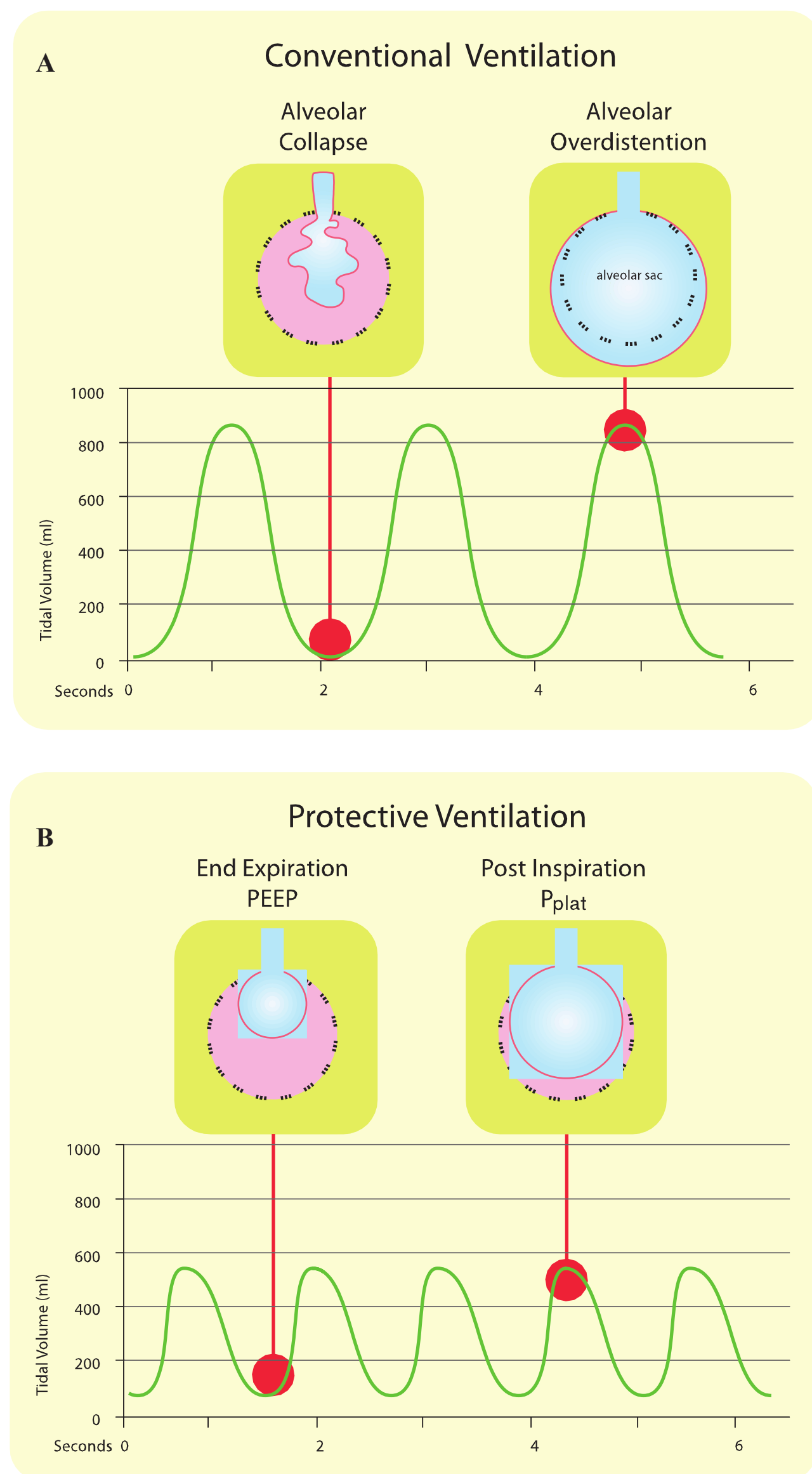


FIGURE 4-3 Example of conventional ventilation compared to protective lung ventilation. **A.** At conventional tidal volumes of 10–12 mL/kg, alveoli are overdistended and collapse at end expiration without PEEP. **B.** At protective ventilation tidal volumes of 4–6 mL/kg, there is no overdistention of the alveoli and no alveolar collapse at end-expiration with addition of PEEP.

machine-delivered tidal volume, whereas control mode (or control mechanical ventilation [CMV]) provides ventilation without regard to patient effort. CMV alone has an application solely in deeply sedated or paralyzed patients (mainly in the operating room).

In A/C mode, the ventilator monitors the circuit for the patient to trigger a ventilator-assisted spontaneous breath via flow or pressure. In the absence of that trigger, the ventilator automatically cycles, delivering set tidal volume (TV) or set PIP machine breaths at a predetermined rate (Figure 4-5). All

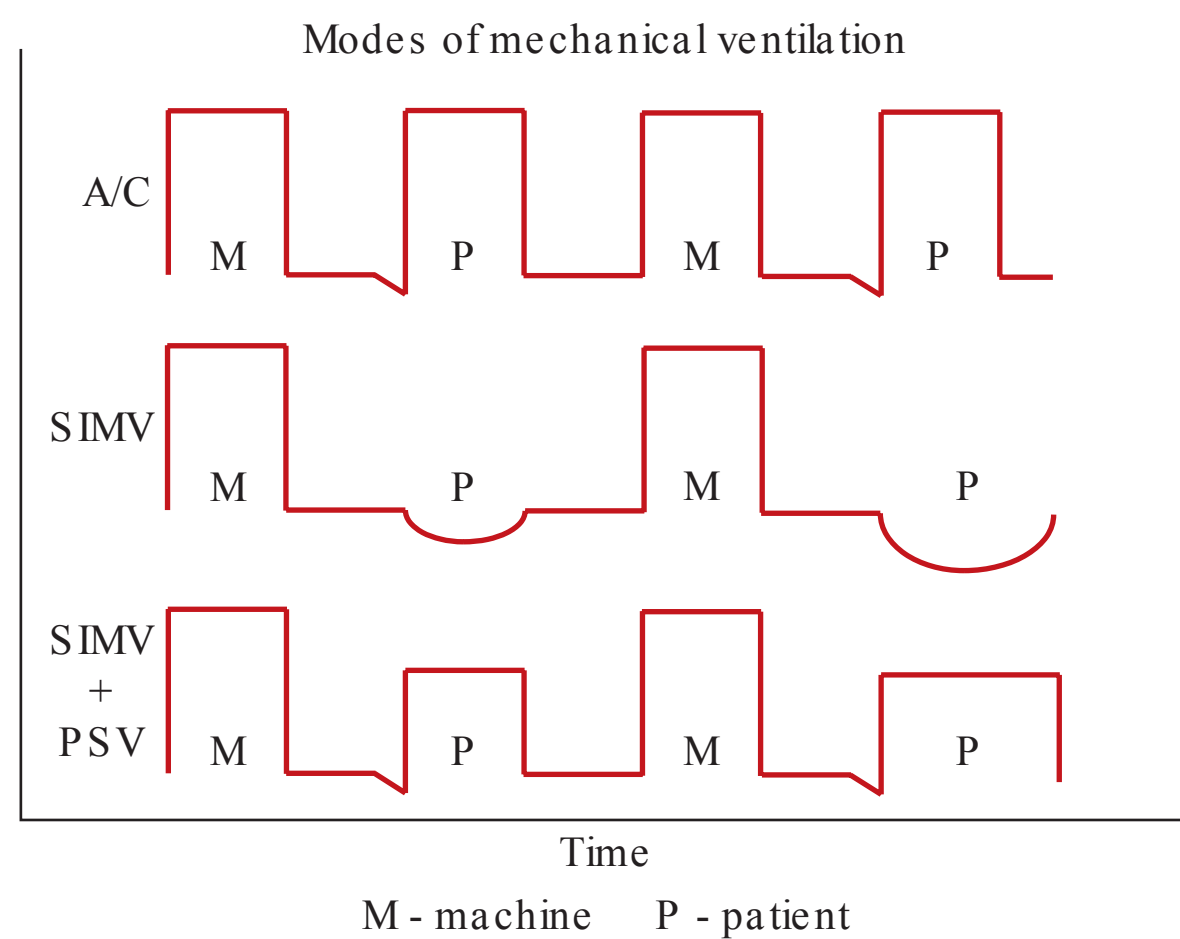


FIGURE 4-4 Modes of ventilation.

breaths in A/C mode receive a set TV or a constant peak pressure for a preset amount of time at a set rate. The patient can have a varying rate but the delivered TV is always the set TV or the PIP is the set pressure, which will deliver a certain tidal volume over a set inspiratory time. A/C mode is appropriate for any patient who requires a secured airway and manifests respiratory fatigue. These patients include, but are not limited to, acute respiratory failure, apneic, pharmacologically paralyzed and deeply sedated patients.

Settings: For A/C mode, the primary settings are respiratory rate, tidal volume or pressure, PEEP, and fraction of inspired oxygen (FiO_2).

Synchronized intermittent mandatory ventilation (SIMV) mode: As in assist-control mode with a set TV, mandatory breaths are patient-triggered, flow-limited, and volume-cycled.

However, breaths taken between mandatory breaths are not supported unless pressure support is added by the practitioner (Figure 4-6).

Settings: Similar to A/C mode, the physician sets an IMV rate, TV, PEEP, and FiO_{2s} to determine a minimum minute ventilation as well as the optional PSV for breaths taken between mandatory breaths.

PSV augments spontaneous breathing with a set inspiratory pressure while the patient determines the TV and respiratory rate. The negative pressure generated by the patient opens a valve that delivers a preset pressure. To keep the pressure constant, the ventilator adjusts the flow rate. A breath is cycled off by setting a percentage of peak flow. For example, if 25% of peak flow is selected, once the flow reaches 25% of the peak flow, the ventilator cycles from inspiration to expiration. As well as augmenting spontaneous breathing, PSV provides assistance to overcome the resistance of the tubing of the ventilator circuit. It is the authors' recommendation that PSV always be added to SIMV.

Settings: The physician sets the PSV generally between a range of 0 and 35 cm H_2O with an average starting value of 5–10 cm H_2O and FiO_2 , with or without PEEP. It is essential to set a rate alarm in those patients who are ventilated by PSV alone because there is no guaranteed minute ventilation. In addition, a percentage of peak flow must be selected to terminate a breath, as discussed earlier.

CPAP is another mode for spontaneous breathing patients. Patients who are able to generate an acceptable minute ventilation can undergo a trial of CPAP. It is frequently used during spontaneous breathing trials. CPAP should equal the amount of PEEP, between 2 and 5 cm H_2O , to prevent loss of alveolar recruitment, atelectasis, and hypoxia. CPAP is also added to decrease the work of breathing (Figure 4-7). The recommended CPAP is 5 to 10 cm H_2O .

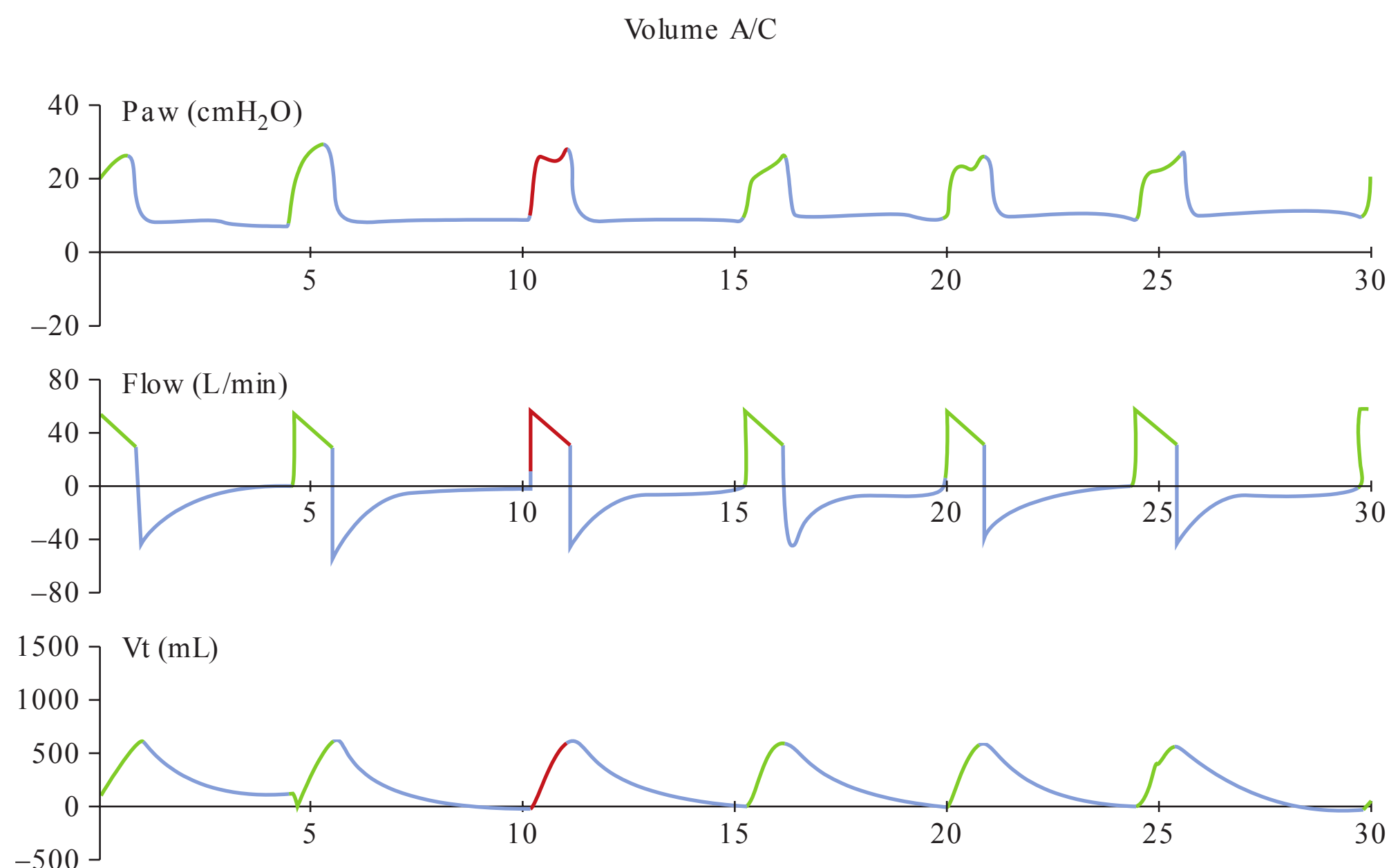


FIGURE 4-5 A/C mode.

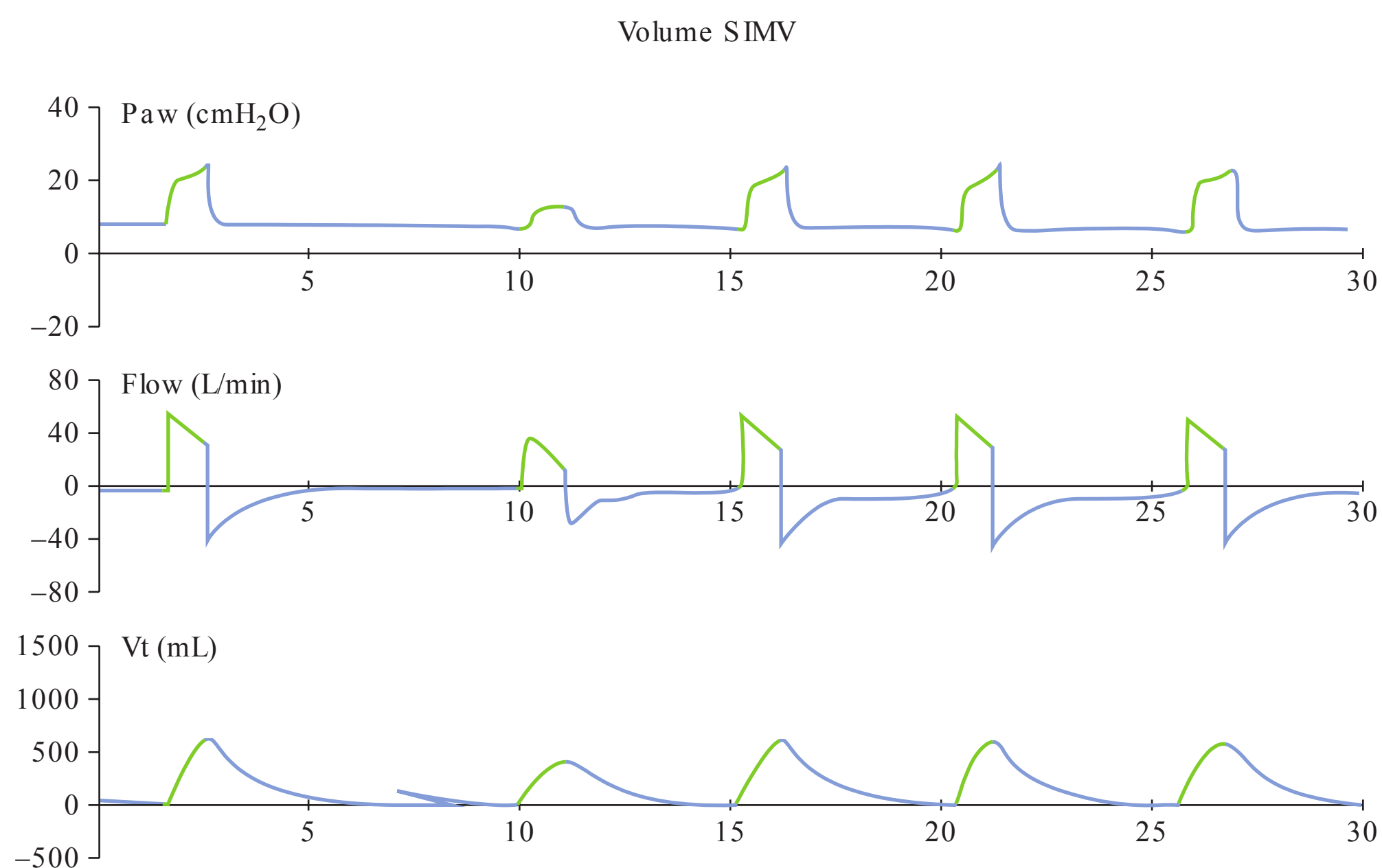


FIGURE 4-6 SIMV mode.

TARGET OF VENTILATION

After a mode has been selected, the mechanism of breath delivery must be determined: inflating the lungs to a predetermined value, either volume or pressure. Over the years, various terms have been used for the type of mechani-

cally delivered breath: targeted, controlled, and cycled. These terms are all interchangeable. For ease of discussion, the term “target” will be used hereafter.

Volume-targeted MV delivers a set TV regardless of the pressures required. Throughout lung inflation, the gas in a volume-assisted breath exerts different pressures in the

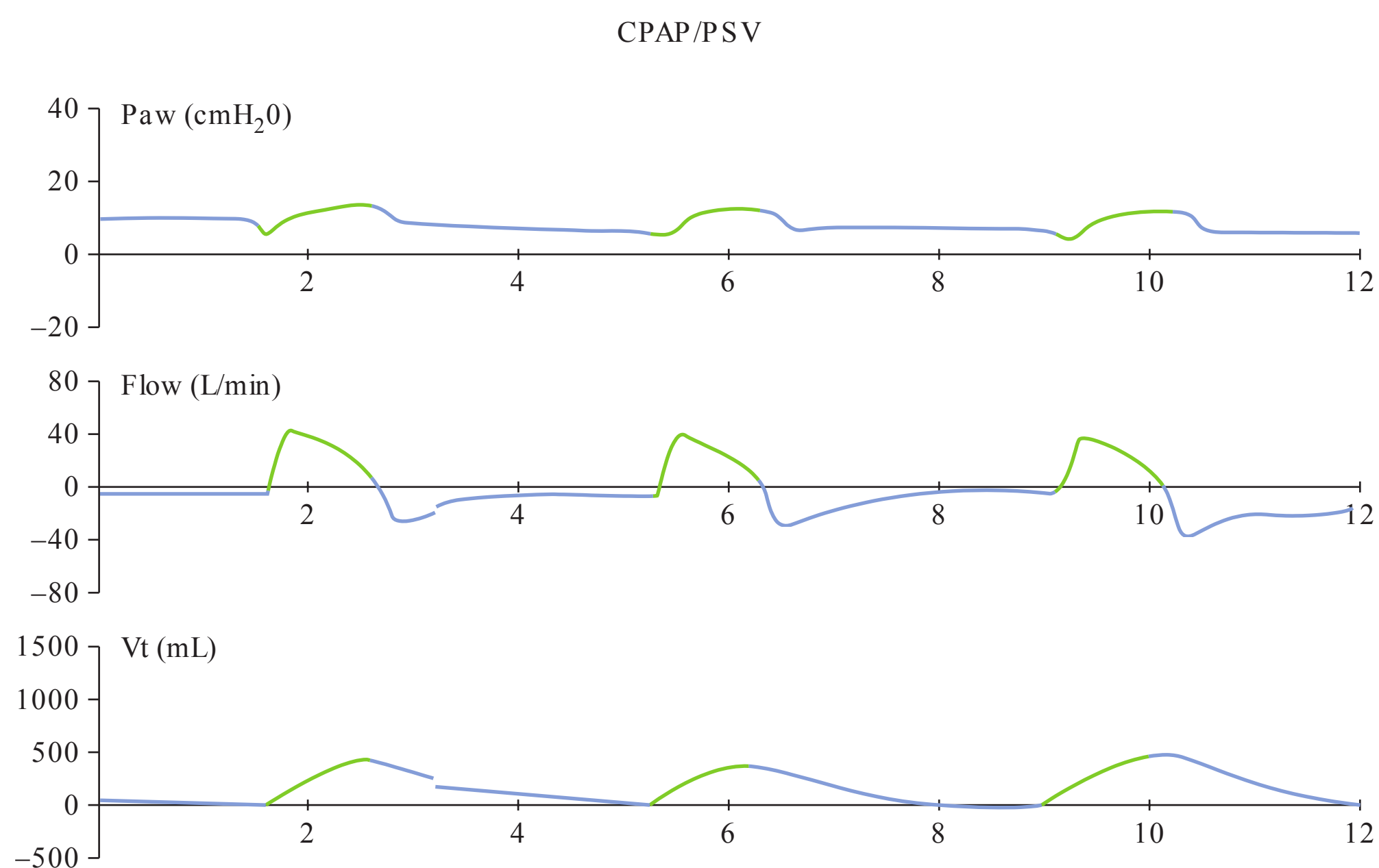


FIGURE 4-7 CPAP/PSV mode.

proximal airways than in the alveoli. The pressure in the proximal airways is a function of resistance; the higher the resistance, the greater the pressure needed to deliver the set volume to the lungs. The pressure in the distal airways is a function of compliance. In disease states in which compliance is decreased, increased pressures are required to achieve the desired tidal volume.

For pressure-targeted ventilation, the ventilator will deliver variable or intermittent flow to maintain a predetermined inspiratory pressure that is equivalent to or lower than P_{plat} to achieve gas delivery. This setting aims to distribute adequate pressures and reduce alveolar overdistention, which can be achieved through precise tailoring.¹² Given that the pressure is constant, resulting in variable tidal volumes, the patient may experience hypoventilation or volutrauma due to variations in minute ventilation. Hence, any alteration in the respiratory circuit such as ETT/airway resistance or lung compliance can lead to hypoventilation or VILI. This variability requires more intensive monitoring such as instituting TV and minute ventilation alarms, close evaluation of the respiratory circuit, and critical decision making by the physician.

Pressure-targeted ventilation is mainly reserved for patients with increased P_{plat} and is recommended to limit VILI or allow healing in ALI/ARDS. All things considered, pressure-targeted ventilation is an option worth considering for specific scenarios. Currently, no study exists demonstrating that one mode is superior to another; however, to ensure patient safety, physician familiarity with a specific mode is more important than modality.

OXYGENATION VERSUS VENTILATION

With regards to basic mechanical ventilator modes and settings, oxygenation is mainly a function of FiO_2 and PEEP. Increasing the PEEP decreases intrapulmonary shunting and increases alveolar recruitment. An increase in FiO_2 supplies the substrate for those two advantages. One approach is to set the FiO_2 at 1.0 and increase the PEEP in increments of 2 to 3 cm H_2O every 10 to 15 minutes until oxygenation goals are met, followed by quickly titrating the FiO_2 down to less than 60% to prevent oxygen toxicity that has been seen in animal models of lung injury. Further, attention should be paid to oxygen delivery (DO_2) and the variables involved in its determination: $\text{DO}_2 = \text{Cardiac Output} \times (1.34 \times \text{hemoglobin saturation} \times S_a\text{O}_2) + (0.0031 \times \text{PaO}_2)$.

The role of ventilation is to maintain adequate Pco_2 and, therefore, pH. This is manipulated primarily by controlling respiratory rate and tidal volume. The goal is to keep the pH between 7.3 and 7.4 unless following the principle of permissive hypercapnea. Rate has a greater influence on Pco_2 than TV; however, an increase in either will cause a decrease in the pH. In addition to an acceptable pH and Pco_2 , the goal should be to maintain $P_{\text{plat}} < 30$ cm H_2O and minimize auto-PEEP.

INITIAL SETTINGS

Finally, the physician must determine the remaining variables. The variable settings most commonly found on a ventilator are PEEP, FiO_2 , respiratory rate, tidal volume, and inspiration flow rate and inspiration time (IT). Additional settings include the trigger sensitivity setting (flow vs. pressure), and rise time in certain modes of MV. Although recommendations will be made regarding *initial* settings, as the patient's condition changes, the settings may need to be adapted, as well.

Positive pressure applied at the end of expiration is PEEP. Its main function is to overcome the tendency of alveolar collapse and is usually set between 5 and 10 cm H_2O . PEEP can have adverse consequences. Increased intrathoracic pressure impedes venous return and decreases preload, leading to systemic hypotension. Thus, caution should be exercised with PEEP values greater than 10 cm H_2O . At times PEEP values greater than 10 cm H_2O are required to maintain adequate oxygenation.

FiO_2 is usually set at 1.0 (100% oxygen) initially, but the general recommendation is to titrate it down shortly thereafter to maintain a PaO_2 greater than 60 mm Hg or SpO_2 greater than 92% to prevent the theoretical risk of oxygen toxicity. A recent multi-center cohort study of 6326 admitted patients to the ICU after out-of-hospital cardiac arrest with a Po_2 greater than 300 mm Hg was seen as an independent risk factor with increase in mortality as compared to the group with normoxia or hypoxic.¹²

In the ARDS Network trial, lower tidal volumes decreased the incidence of VILI and barotrauma. In that study, the tidal volume goal for lung-protective ventilation was 4–6 mL/kg PBW. In another study, it was shown that tidal volumes greater than 9 mL/kg PBW are a risk factor for development of VILI.¹⁴ The authors recommend an initial value in non-ARDS patients of 6 to 8 mL/kg PBW as needed to maintain P_{plat} pressure of less than 30 cm H_2O .

Normal physiologic inspiratory to expiratory (I:E) ratio is approximately 1:3, whereas patients on MV typically are set to 1:2. This can be manipulated by changing the respiratory rate, TV, and the IT or flow rate.

An assisted breath can be triggered by a timer (set rate) on the ventilator or by patient effort. One of two factors can be used to sense patient effort and trigger the breath to be delivered: a decrease in airway pressure or sensing inspiratory flow generated by the patient. If pressure is selected for the trigger, the threshold pressure is usually set at a level of - 1 to - 2 cm H_2O . PEEP adds to the total amount of force needed to trigger a breath. For example, if the trigger pressure is - 2 cm H_2O and the PEEP is 5 cm H_2O , the patient must generate a pressure of - 7 cm H_2O , a considerable amount of force from a patient in respiratory failure. If the trigger sensitivity is set for inspiratory flow, then generally a setting of 2 L/min is used because this amount does not generate significant airway pressures and should require less effort by the patient.¹⁵ Practitioners should be aware that if the sensitivity is set too high it could lead to false triggering or auto-triggering.

SPECIFIC SCENARIOS

Obstructive lung diseases such as asthma and COPD are commonly encountered in the ED. The specifics of MV in these patients primarily revolve around the prevention intrinsic PEEP/auto-PEEP (also termed dynamic hyperinflation). By definition, obstructive lung disease involves problems that result in prolonged exhalation exhibited by their decreased FEV₁. If the ventilator delivers a breath before the patient is able to exhale back down to baseline, breath stacking occurs, resulting in increased lung volumes and pressures. These can then result in decreased venous return, leading to hypotension and increased morbidity and mortality.

To prevent breath stacking, a lower respiratory rate (6 to 10 breaths/min), an increased flow rate (around 80 to 100 L/min initially), and lower tidal volumes (5 to 7 mL/kg PBW) should be employed to increase the I:E ratio. These changes are not without consequences. The reduction in minute ventilation with a decreased respiratory rate and TV can lead to hypercapnia, causing a respiratory acidosis. Additional consequences of hypercapnia include increased cerebral blood flow (and subsequent increase in intracranial pressure [ICP]), myocardial depression, arrhythmias, and abnormal cellular metabolism. Overall, these decreases in arterial pH are generally well tolerated and much less harmful than the complications of auto-PEEP. The pH may require intervention when it is less than 7.20 and clinically indicated. While hypercapnia can be a powerful central stimulus to increase respiratory rate, this response is usually blunted with medications such as opiates or other sedatives, but may be so strong as to require chemical paralysis. However, paralytics should be used with caution in conjunction with steroids due to the risk of the steroid-induced neuropathies.¹⁶ While recent evidence has shown that a short trial of a paralytic did not increase morbidity in ARDS patients, this has remained a debated topic.¹⁷

The goal for patients with brain injury, encephalopathy, and increased ICP is to maintain adequate cerebral perfusion pressure. Although hypercapnia and acidosis can increase ICP, prophylactic hyperventilation has been shown to be deleterious in patients with head injuries and is no longer recommended.²⁰ Settings should focus on adequate oxygenation, normalizing pH, and optimizing hemodynamic stability. If a patient deteriorates secondary to worsening neurologic pathology, hyperventilation can be instituted briefly to allow time for other therapies to take effect. This application of hyperventilation should not extend past 1 to 2 hours.

TROUBLESHOOTING MECHANICAL VENTILATION

It is essential to establish a quick and logical approach to the unstable patient on MV when the ventilator alarms are sounding and the patient is hemodynamically compromised. VILI, MV-induced cardiovascular collapse, and patient-ventilator dyssynchrony are the primary concerns.

The first critical action is to disconnect the ventilator tubing from any patient in the presence of ventilator alarms and cardiovascular collapse. Removing the ventilator from the equation limits the number of variables in solving this life-threatening challenge and immediately eliminates it as a primary culprit. Ventilations with a bag-valve system can confirm ETT placement with an end-tidal CO₂ device, estimate the degree of airway resistance, and observe the chest or abdomen rise with each ventilation. These steps eliminate immediate threats of extubation, ETT obstruction, and increased airway resistance.

If an end-tidal CO₂ device and auscultation are not sufficient in detecting appropriate tube placement, direct visualization with direct laryngoscopy is the gold standard. If evidence of extubation is discovered, the tube should be removed and the patient prepared for reintubation.

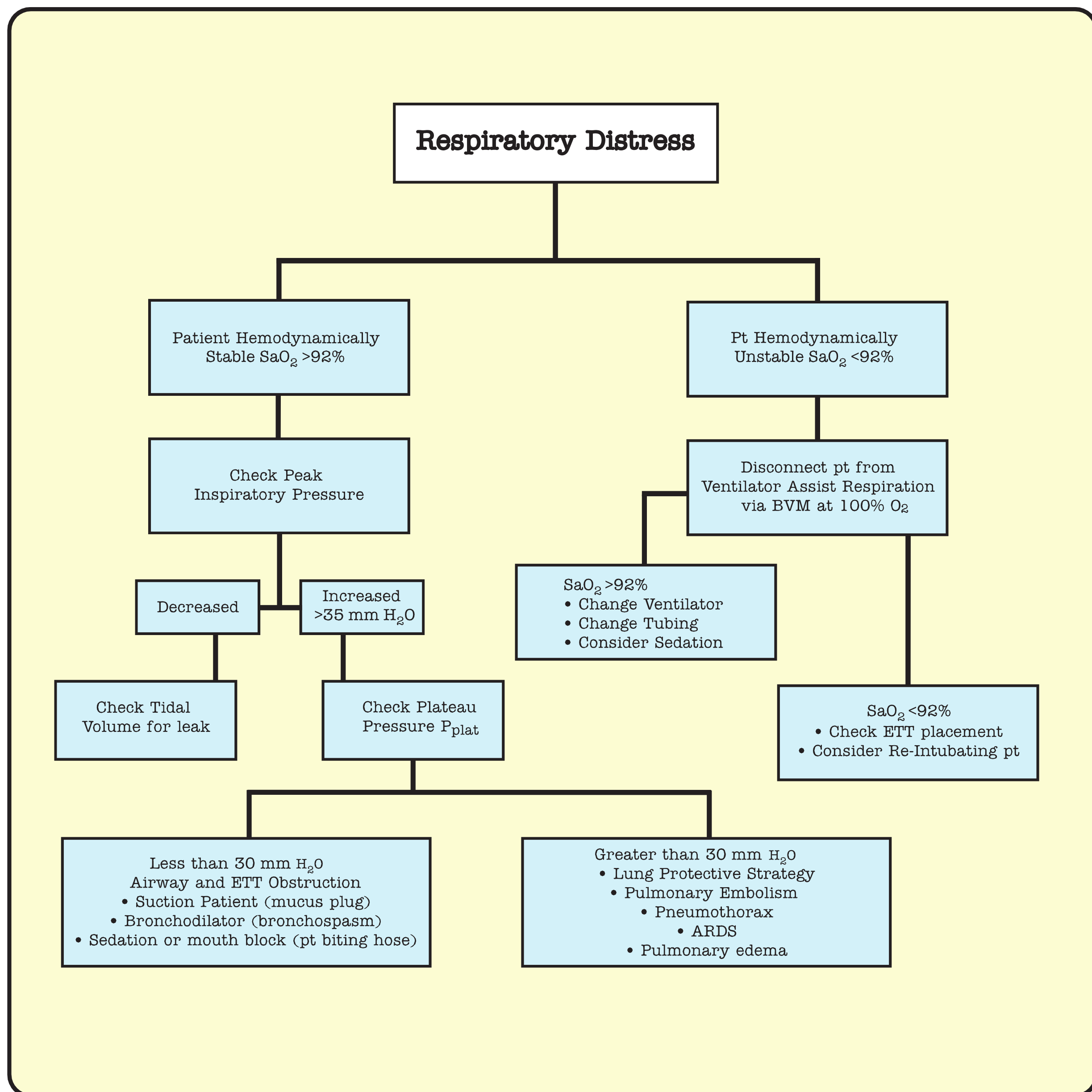
Endotracheal tube obstructions due to mucus plug, blood clot, or aspirate are quickly deduced by looking at ventilator waveforms and by utilizing airway-intubating stylets (gum elastic bougie). This requires prompt extubation and reintubation. Difficulty during bag-valve ventilations is linked to increased airway resistance and reduced compliance. The differential in these cases includes auto-PEEP, pneumothorax, main stem intubation, and worsening reactive airway disease. Utilization of bedside ultrasound or portable chest X-ray can quickly identify the etiology of the reduced compliance in most of these cases. Emergent diagnosis of tension pneumothorax and immediate intervention with needle thoracostomy can be lifesaving.

Caution should be maintained for patients with reactive airway disease and dynamic hyperinflation or intrinsic PEEP. Rescue ventilations can further exacerbate this condition if ventilation is too fast (greater than 10 breaths/min), or too large (more than 500 mL tidal volume). Limiting the rate and size of the tidal volume breaths increases the expiratory time and permits enhanced lung emptying of trapped volume present in intrinsic PEEP. As previously stated, a crystalloid bolus of 500 mL to 1 L should be administered over 5 to 15 minutes with consideration for appropriate sedation.

It is critical for providers to understand that patient agitation suspected of causing patient-ventilator dyssynchrony should be a diagnosis of exclusion. Treating the unstable, agitated patient on MV with paralysis or heavy sedation without applying a quick and logical approach to exclude the MV as a cause or other life-threatening causes can be a preterminal event. When the respiratory demands of the patient are not met by MV, patient-ventilator dyssynchrony occurs, and it is one of the more common problems of MV.²¹ Physiologic issues, such as neurologic derangements, hypoxia, hypercapnia, and inappropriate ventilator settings, need to be investigated primarily. Last, dyssynchrony can also be an issue of inadequate analgesia or sedation—again, a diagnosis of exclusion. One study has shown that adequate postintubation anxiolysis and analgesia is commonly overlooked by emergency physicians²² (Table 4-2).



TABLE 4-2: Troubleshooting Ventilator



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Airway Pressure Release Ventilation

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Editor Note

For those who have limited exposure to **airway pressure release ventilation** (APRV), it may help to conceptualize the following discussion through two paradigms. One is to consider high pressure (P_{High}) similar to a higher pressure CPAP with periodic releases or breaks. When pressure is held over time, the pressure may dissipate over the lung field. As the pressure dissipates and alveoli begin to open, the wall tension of connected (unrecruited) alveoli is changed, facilitating their recruitment. The time over which the CPAP (P_{High}) is held is the “Time high” (T_{High}). The second paradigm is visualizing blowing up a balloon and holding it by the balloon neck. The P_{High} could be considered the pressure within the inflated balloon. P_{Low} is the lower pressure outside the balloon. The T_{high} could be considered the amount of time the neck of the balloon is held closed. The T_{Low} could be analogous to how long the neck of the balloon is released. Using the inflated balloon analogy, how much air leaves the balloon (and thus how much remains) is a factor of the pressure differential between the inside of the balloon and the outside, how long the neck of the balloon is released, and extrinsic forces being applied to the outside of the balloon. So, if the neck of an inflated balloon were released for 30 seconds, most of the air would leave the balloon as the pressures equilibrated and the “patient would derecruit.” If the neck of the inflated balloon were to be released for 0.5 seconds, there would be some release of air, but a significant amount would still be retained within the balloon. As will be explained later, this is why there is CO_2 release without derecruitment and why the traditional setting of P_{Low} is zero. Further, extrinsic factors can impact how much air is released during a given T_{Low} . For example, as abdominal hypertension progresses to abdominal compartment syndrome, the abdominal contents press against the

diaphragm, causing more air to be released during a given T_{Low} , similar to the inflated balloon being compressed while releasing the neck of the balloon.

Another concept to consider with APRV is that the pressure (P_{High}) administered during the T_{High} is similar to CPAP in that the patient can breathe during P_{High} . As will be discussed more fully, the patient's native breaths initially will be ineffectual in releasing CO_2 and most of the ventilation will occur during the set T_{Low} phase. However, as the patient gets stronger, more CO_2 will be released during the patient's native breaths. This allows for weaning, as the P_{High} will be dropped and the T_{High} will be extended until the patient achieves a traditional CPAP setting and can be extubated. An important note is that T_{Low} is not adjusted as part of the weaning process except under specific conditions that are explained in full later. Further, note that certain ventilators have software that automatically increases T_{Low} if a patient breath occurs at the terminal component of T_{High} . In our opinion, this could lead to significant derecruitment as patient dynamics are not considered, there may be no alert or warning of this occurring, and the clinician may be unable to override this feature. Theoretical benefits of allowing native breaths (without mechanical support) during the T_{High} segment revolve around preventing diaphragmatic deconditioning and improved posterior lung field recruitment. We hope this assists with the ensuing discussion, provided by world-renowned experts in the field.

INTRODUCTION

Airway Pressure Release Ventilation (APRV) is a pressure limited, time-cycled mode with a framework consisting of pressure, time, flow, and volume. The configuration of these elements creates a mechanical breath profile (MB_p) in

which the upper pressure (P_{High}) is sustained for an extended period of time (T_{High}), creating a near continuous positive airway pressure (CPAP) phase (approximately 90% of the total cycle time); the lower pressure (P_{Low} , commonly set to zero) provides a pressure interruption of the P_{High} (CPAP phase) for a brief period of time (T_{Low}), generating a release phase (approximately 10% of the total cycle time). When considering alveolar mechanics, the extended CPAP phase promotes alveolar recruitment and stability while the release phase limits derecruitment and alveolar instability by establishing a near continuous static inflation. Additionally, the release phase controls carbon dioxide (CO_2) clearance in non-spontaneously breathing patients and augments CO_2 clearance in patients capable of spontaneously breathing.

Conceptually, APRV may be viewed as a time-based mechanical ventilation strategy that configures the MB_p to accommodate the underlying lung physiology by controlling lung time constants. For example, in acute lung injury (ALI) time constants are prolonged for recruitment.^{1,2} When comparing the MB_p of conventional modes and APRV, the MB_p of a conventional ventilation mode with a rate of 10 breaths per minute yields a total cycle time of 6 seconds. Within the 6-second respiratory cycle, the inspiratory phase (necessary for lung recruitment) typically occupies < 1 second with the excess of 5 seconds spent in the expiratory phase, relying on positive end expiratory pressure (PEEP) to prevent derecruitment. Conversely, the MB_p of APRV with the rate of 10 breaths per minute yields a similar 6-second total cycle time; however, > 5 seconds is spent at the CPAP (inspiratory) phase maximizing lung recruitment and < 1 second spent at the release (expiratory) phase minimizing derecruitment (Figure 5-1). Less than 1 second spent at the inspiratory phase in conventional modes may not be sufficient to establish

alveolar recruitment and stability, which has been shown to cause further lung injury through cyclic opening and closing and increased stress risers.³ However, APRV with a prolonged CPAP phase has been shown to effectively recruit and stabilize collapsed alveoli with a decrease in alveolar and alveolar duct strain, lung injury and inflammation.

Mathematically, this can be expressed as the pressure-time integral where P = airway pressure (in $\text{cm H}_2\text{O}$), t = time (in seconds), T_{insp} = the time at the beginning of inspiration, and T_{exp} = the time at end expiration. The longer the pressure-time integral, alveolar stability for a greater portion of the respiratory cycle increases (Equation 1).

$$P/T_p = \int_{T_{\text{insp}}}^{T_{\text{exp}}} P dt$$

Because the user is capable of infinitely adjusting the configuration of the MB_p in APRV, the acronym “APRV” may be inadequate to describe the setting variations and their impact on the lung. The method of setting APRV described from here is based on over 20 years of clinical experience and supporting clinical and laboratory data.⁴⁻⁹

APRV SETTINGS

Pressure During the CPAP Phase (P_{High})

The CPAP phase controls end-inspiratory lung volume and is defined as a combination of the P_{High} (expressed as cmH_2O) and the T_{High} (expressed as seconds). Most modes ventilate by increasing airway pressure above a baseline PEEP setting to reach a plateau pressure. In comparison, the CPAP phase of APRV is the baseline pressure and ventilation results from releasing the P_{High} towards the P_{Low} where a portion of the

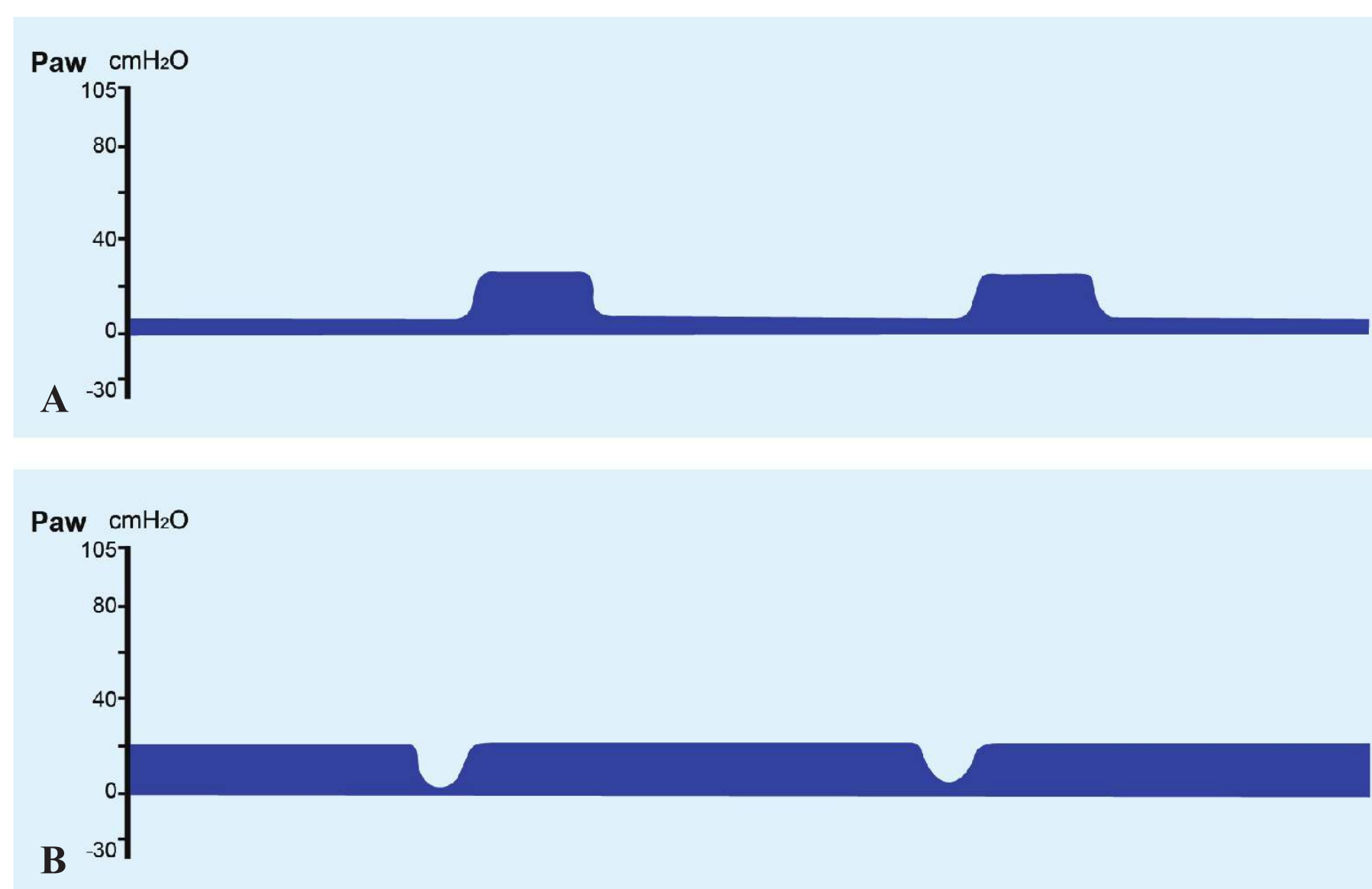


FIGURE 5-1 Comparison of Mechanical Breath Profiles (MB_p) Between Conventional Ventilation and APRV. **A.** Displays the MB_p of conventional ventilation with a rate of 10 breaths/minute. **B.** Displays the MB_p of APRV with similar rate of 10 breaths/minute. (Used with permission from Intensive Care On-Line Network (ICON)).

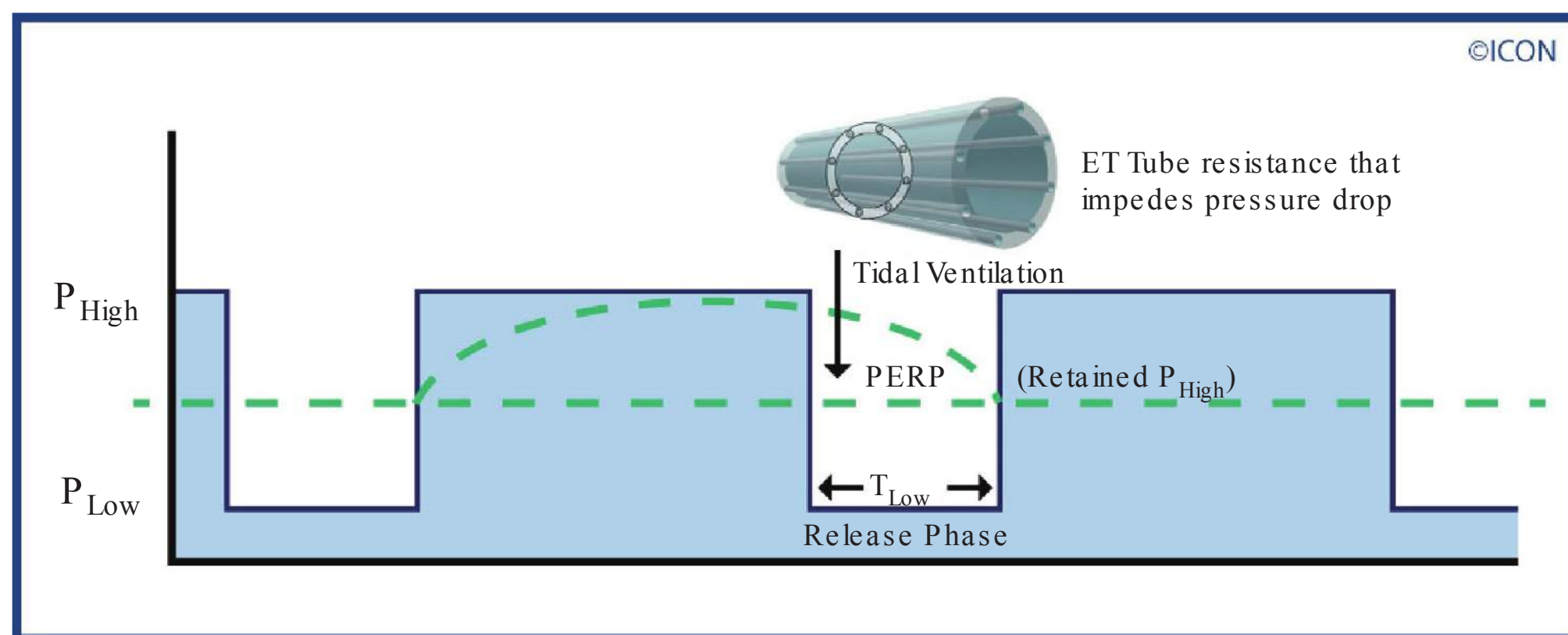


FIGURE 5-2 Positive end-release pressure (PERP) within the P_{High} . The artificial airway creates a majority of the resistance impeding the pressure drop from P_{High} toward P_{Low} . The T_{Low} uses time to retain a portion of the P_{High} , thus retaining adequate end-expiratory lung volume. (Used with permission from Intensive Care On-Line Network (ICON)).

P_{High} is retained as positive end release pressure (PERP), similar to PEEP (Figure 5-2).

The recoil of the thorax and abdomen facilitates tidal ventilation with APRV and is increased in patients with higher thoraco-abdominal elastance from obesity or edema/ascites when the P_{High} is released. These factors are important when determining the optimal duration (T_{Low}) of the release phase. Because the P_{High} is released rather than increased for ventilation, total lung volume decreases as opposed to increasing in conventional ventilation, thereby limiting tidal overdistention. Baseline lung volume is typically higher in APRV as more alveoli share in the volume change as a result of improved homogeneity⁸ and may be one of the key mechanisms in preventing lung injury.

It has been shown that alveolar recruitment is achieved by the combination of pressure and time¹ and the CPAP phase in APRV recruits alveoli, enhancing oxygenation and CO_2 diffusion. Ideally, the P_{High} is set to maintain lung inflation along the steep portion of the pressure-volume curve between functional residual capacity (FRC) and total lung capacity (TLC), to minimize the elastic work of breathing. When set to the appropriate lung volume, unassisted spontaneous breaths occur without excessive work of breathing (WOB) because the extremes of lung volume are avoided.

Although P_{High} pressures generally range from 20 to 35 cm H_2O for adults, 20 to 30 cm H_2O for pediatrics and 10 to 25 cm

H_2O for neonates, a $P_{\text{High}} > 35$ cm H_2O may be required to counter increased thoraco-abdominal elastance^{10,11} and the use of esophageal pressure manometry may be considered to determine transpulmonary pressure.¹² Because pressure requirements are less when maintaining lung volume rather than recruiting a collapsed lung^{13,14} against opposing forces (i.e., large abdomen and edema), early application of APRV may be key to minimizing airway pressure requirements.¹⁵ Ultimately, using APRV preemptively rather than as a rescue strategy prevents lung collapse; preserves surfactant function; and reduces pulmonary edema, pulmonary inflammation, and histopathology.^{4-8,16}

Although APRV is used as a primary mode of ventilation, transitioning to APRV may occur from a pressure-based mode, dual control mode (i.e., PRVC), volume-based mode, or High Frequency Oscillatory Ventilation (HFOV; Table 5-1).

Time During the CPAP Phase (T_{High})

The T_{High} (expressed in seconds) controls alveolar (diffusive) ventilation, inspiratory time constants and end-inspiratory lung volume and is ideally set to create the optimal CPAP phase for maximum lung recruitment.^{1,13,17} The time-dependent nature of recruitment dictates that sufficient time at an optimal pressure is necessary to recruit alveoli. Alveolar recruitment increases alveolar surface area and optimizes gas diffusion, which minimizes stress-concentrators³ over a more homogenous lung.^{1,8,18-23}



TABLE 5-1: P_{High} Settings Based on Previously Published Clinical Guidelines⁹

	Adults	Pediatrics	Neonates
APRV as Initial Mode (P_{High} Setting)	20–35 cm H_2O	20–30 cm H_2O	10–25 cm H_2O
Transition from Pressure/Dual Targeted Mode	Set initial P_{High} to Peak Pressure (inspiratory pressure plus PEEP)		
Transition from Volume Mode	Set initial P_{High} to the Plateau Pressure		
Transition from HFOV	Set initial P_{High} to 2–4 cm H_2O above the Mean Airway Pressure in HFOV		

APRV may be set as the initial mode or transitioned from another mode. Note that the P_{High} may require adjustment based on lung volume at time of transition.


TABLE 5-2: T_{High} Settings Based on Previously Published Clinical Guidelines⁹

T_{High} Setting	Adults	Pediatrics	Neonates
APRV as Initial Mode	4–6 seconds	3–5 seconds	1.5–2 seconds
CPAP Phase $\geq 90\%$	Highly recruitable lung		
CPAP Phase 70–80%	Less recruitable lung		

T_{High} is based on patient range and the desired CPAP phase.

Combining diffusive and convective gas exchange in APRV provides a more efficient form of ventilation than conventional modes with lower minute ventilation for equivalent CO_2 clearance,^{18–23} resulting in less dynamic strain on the lung.^{24–26} Because the transfer of pressure from the proximal airways to the alveoli is attenuated by the artificial airway, the prolonged T_{High} allows airway-alveolar pressure equilibration for improved recruitment, alveolar stability and near continuous CO_2 transfer.²⁷ During the CPAP phase with a prolonged T_{High} , even in the absence of breathing, alveolar CO_2 diffuses from the distal air space into the large airways and trachea, allowing a large concentration of CO_2 to be eliminated over a very brief period of time with each release phase. Thus, even though the minute volume is typically lower in APRV than in conventional modes of ventilation, CO_2 removal is more efficient due to increased alveolar (diffusive) ventilation.^{18–23} Cardiogenic motion further aids gas mixing by agitating CO_2 molecules during the CPAP phase, causing CO_2 to reach the distal airways and trachea.^{28–32} The subsequent release phase is a transition from diffusive to convective gas movement and the combination results in a 30% increase in CO_2 efficiency, which offloads a majority of the metabolic load associated with ventilation. Therefore, the potential for excessive metabolic WOB^{18–23} effectively reduces the metabolic burden by proportioning the work between the ventilator and the patient.

The respiratory frequency in APRV is determined by this formula: $60 \text{ seconds} / T_{\text{High}} + T_{\text{Low}}$ (i.e., $60 / 5.5 + 0.5 = \text{rate } 10 \text{ breaths/minute}$) and is set based on the recruitability of the lung and patient range (Table 5-2). A CPAP phase can be calculated by using this formula: $T_{\text{High}} / T_{\text{Total}} (T_{\text{High}} + T_{\text{Low}}) \times 100$ (i.e., $5.5 / (5.5 + 0.5) \times 100 = 91.6\%$) and is critical in reducing stress-concentrators, edema prevention, and surfactant and epithelial layer integrity.^{4,5} A CPAP phase of at least 90% is ideal in most patients; however, patients with fibrosis or underdeveloped lungs (i.e., premature neonates) typically

require more bulk ventilation, resulting in a reduced T_{High} and CPAP phase of 70% to 80%.

Pressure (P_{Low}) and Time (T_{Low}) During the Release Phase

The Release Phase is defined as a combination of the P_{Low} (expressed as cmH_2O) and the T_{Low} (expressed in seconds) that controls the end-expiratory lung volume, analogous to PEEP and convective (bulk) ventilation.

Some clinicians believe that setting a P_{Low} at 0 cmH_2O in APRV results in alveolar instability and collapse, similar to a PEEP of 0 cmH_2O in conventional modes. However, unlike conventional modes, the release phase in APRV is brief, which stabilizes alveoli and prevents collapse by two mechanisms: (1) the brief release phase maintains PERP, even with the P_{Low} set at 0 cmH_2O ; and (2) the release time (T_{Low}) is less than the collapse time constant of the alveolus preventing alveolar collapse.

Coupled with the brief release phase, artificial airway attenuation of gas flow (typically delaying expiratory time constants three-fold) results in the lung retaining a portion of the pressure (P_{High}) during the release phase, making time (T_{Low}) the controller of end-expiratory lung volume.^{33,34} Retaining a fraction of the P_{High} as end-expiratory lung volume prevents alveolar collapse, negating the need to set a $P_{\text{Low}} > 0$ cmH_2O (Figure 5-2). The T_{Low} is typically sub-second and the inherent resistance of the artificial airway initially slows the expiratory gas flow and pressure drop from P_{High} towards P_{Low} (Figure 5-2). A P_{Low} set to 0 cmH_2O allows for rapid expiratory bulk gas movement during the initial release, optimizing CO_2 removal within a briefly confined time period (10% of the respiratory cycle).

The ideal PEEP or setting a P_{Low} greater than 0 cmH_2O using conventional expiratory time necessary to prevent alveolar


TABLE 5-3: T_{Low} Settings Based on Previously Published Clinical Guidelines⁹

T_{Low} Setting	Adults	Pediatrics	Neonates
Initial T_{Low} Setting	0.35–0.6 Seconds	0.2–0.5 Seconds	0.2–0.3 Seconds
Normal-Acute Restrictive Lung Disease	T_{Low} set to terminate at 75% of PEFR		
Obstructive Lung Disease	T_{Low} set to terminate at 25–50% of PEFR		

Data demonstrate that a T_{Low} set to terminate at 75% of PEFR (T-PEFR) retains adequate end-expiratory lung volume without adversely affecting CO_2 elimination.

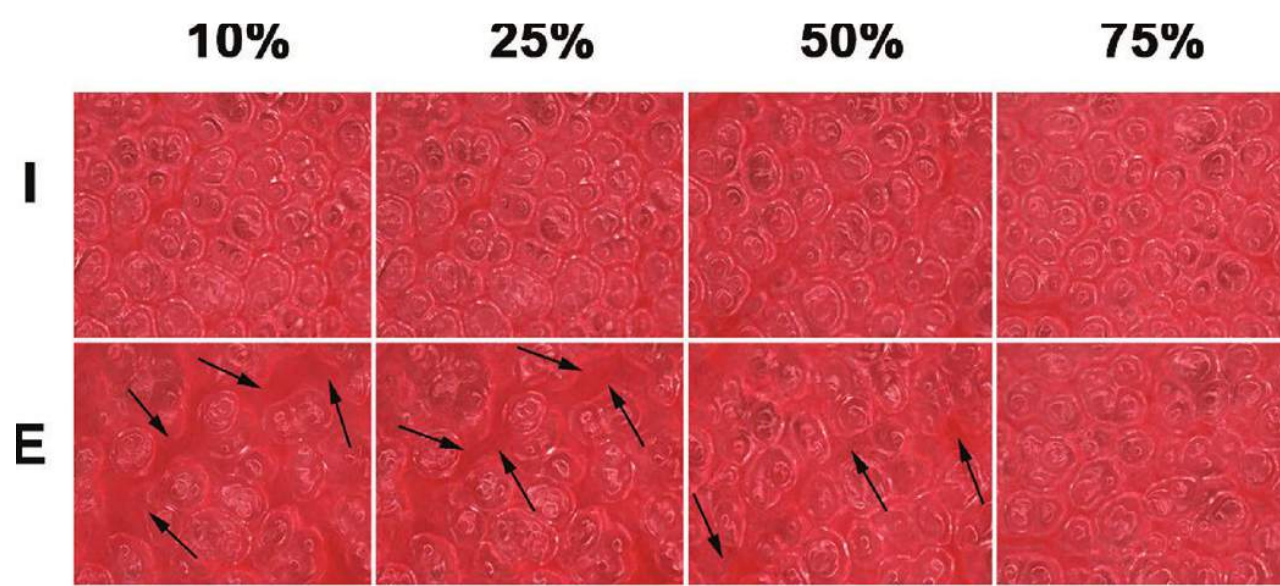


FIGURE 5-3 T_{Low} Termination of PEFR Ranging from 10% to 75%. Alveolar microscopy at 4 different percentages of termination of PEFR. As termination of PEFR percentage increases, alveolar stability increases. I, inspiration; E, expiration; Black arrows illustrate interstitial expansion between aerated alveoli due to alveolar collapse at expiration. A progressive decrease in interstitial expansion and greater number of recruited alveoli occupying the field are seen moving left to right from 10% to 75%. (Used with permission from Intensive Care On-Line Network (ICON)).

collapse during expiration is unknown. However, using PEFR to set the T_{Low} in APRV with a P_{Low} of 0 cmH₂O allows monitoring of the lung physiology to precisely identify the fraction of a second at which to terminate the release, preventing alveolar collapse and maintaining adequate FRC without adversely affecting CO₂ elimination. We have directly shown, using *in vivo* microscopy in an animal model of ARDS, that setting a P_{Low} of 0 cmH₂O with an appropriately set T_{Low} to terminate at 75% of the PEFR (T-PEFR) prevents alveolar collapse and stabilizes end-expiratory lung volume with < 10% change in alveolar volume between the CPAP and release phase and provides alveolar stability that is not achieved in conventional ventilation with PEEP set to 16 cmH₂O.^{2,13,35,36} Conversely, when the T_{Low} was adjusted to a T-PEFR < 75%, alveoli collapse and reopen with greater alveolar volume change between the CPAP and release phase (Figure 5-3).^{8,36}

The T_{Low} ideally controlled in 1/100 second increments, is the duration of the P_{Low} defining the time course of the release phase. Thus the T_{Low} controls the amount of airway pressure (P_{High}) and lung volume to be released and the amount retained as end-expiratory lung volume. APRV has been described as inverse ratio pressure control (IR-PCV). However, the key difference between APRV and IR-PCV is the ability to independently adjust the T_{Low} without affecting the CPAP phase. Further, in comparison to pressure control with a closed expiratory circuit, which does not allow exhalation without elevating circuit pressure and pressure limiting, APRV with an open breathing system permits exhalation at any time in the cycle without the need to raise circuit pressure above the P_{High} .

The *release* controlled with the T_{Low} facilitates the transfer of energy (potential to kinetic) generated in the thoraco-abdominal cavity during the CPAP phase as a result of the elastic deformation. During the release phase, expiratory gas flow through the artificial airway creates an angle of deceleration or flow decay (Figure 5-4) and the resultant flow-time curve (expiratory flow pattern) is analyzed. The T_{Low} is set using a physiologic feedback loop by analysis of the expiratory flow curve. The physiologic condition of the lung can

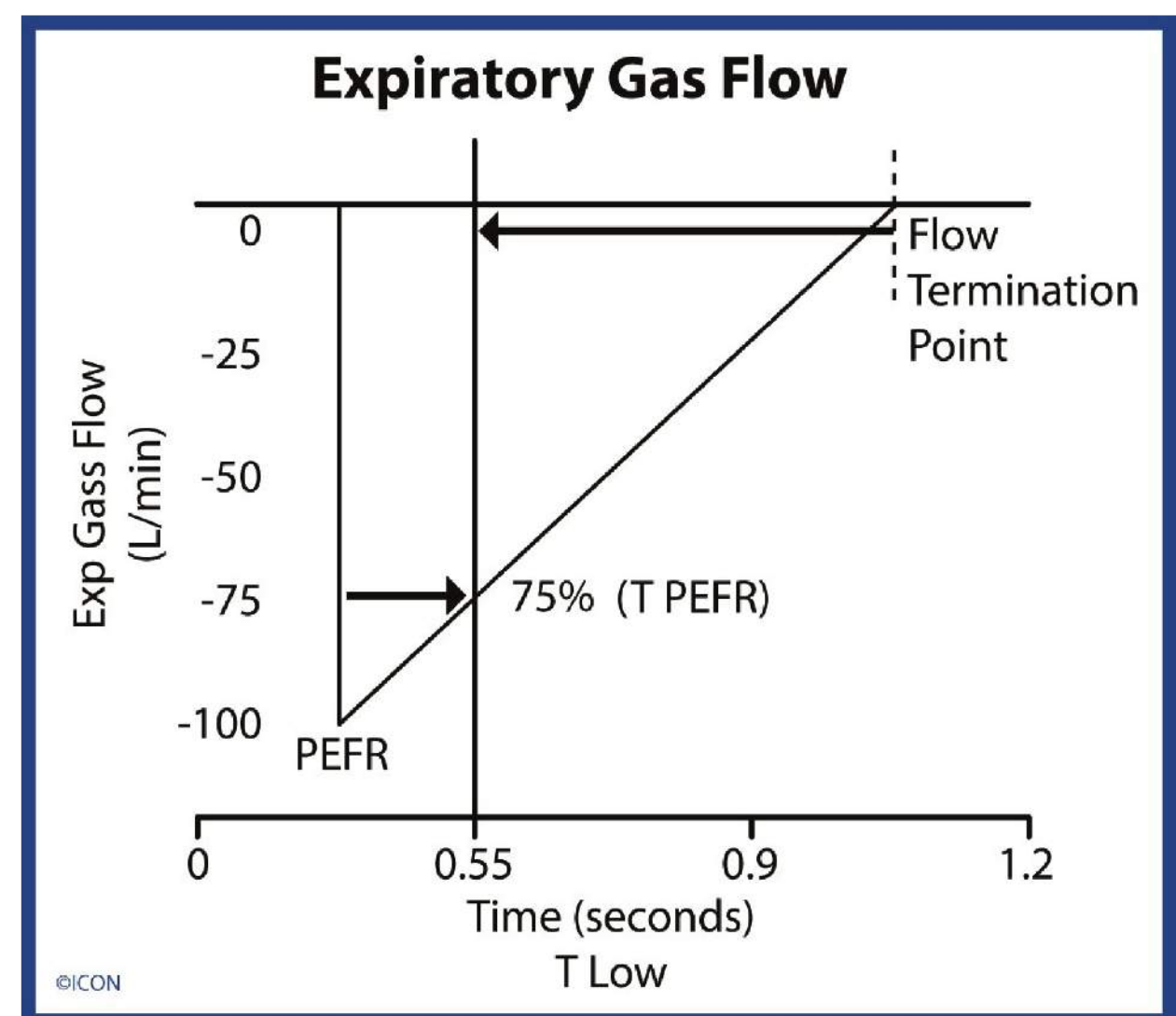


FIGURE 5-4 Expiratory Gas Flow. Expiratory gas flow pattern during APRV demonstrating adjustment of the T_{Low} to terminate the expiratory gas flow at 75% of the Peak Expiratory Flow Rate (PEFR). (Used with permission from Intensive Care On-Line Network (ICON)).

be determined by the angle of the expiratory flow curve. For instance, the sharper the angle of the expiratory flow curve, the more rapid the lung is collapsing and the greater the risk for ALI. The angle of deceleration is more acute in restrictive lung disease (i.e., < 45 degrees) than in obstructive lung disease (i.e., > 45 degrees; Figure 5-4).

The T_{Low} requires frequent analysis and adjustment to maintain optimal released lung volume, which may be affected by changes in thoracic/abdominal elastance, size and position of the artificial airway, secretions in the airway, or any form of obstruction on the expiratory side including the artificial airway, ventilator circuit, and expiratory block of the ventilator. Although an increase in T_{Low} beyond the optimal setting can increase the amount of volume released and transiently increases CO₂ removal, T_{Low} should only be adjusted based on the expiratory flow pattern to maintain T-PEFR 75% rather than to titrate a targeted tidal volume or CO₂ measurement. Inappropriate setting of the T_{Low} may result in hypercarbia if T_{Low} is too brief (> 75% T-PEFR) or derecruitment, alveolar instability, and propagate lung injury if prolonged (< 75% T-PEFR), with a loss in surface area and resultant decrease in diffusive CO₂ clearance.

Initial T_{Low} settings are based on patient range and once set, the expiratory flow pattern must be assessed and confirmed for appropriate termination of 75% of the PEFR (Figure 5-4).

Tidal Volumes

APRV has been associated with tidal volumes larger than those currently believed to be protective³⁷ using conventional ventilation.^{4,5} We have shown that, when APRV is preemptively applied to normal lungs in animals at high risk of developing ARDS, ALI is dramatically reduced.^{4,5} Preemptive APRV with

a resultant tidal volume of ~ 12 cc/kg was superior at lung protection to conventional ventilation using a low tidal volume strategy of 6 cc/kg.⁴ The extended time at P_{High} and minimal time at T_{Low} in APRV maintains lung recruitment over a more homogenous area, resulting in more alveoli sharing the tidal volume load. Therefore, lung volume (not tidal volume) increases as the interdependency of alveoli through collateral channels of ventilation promote stability.^{4,5,8,16,38} Recent data suggest that, despite whole lung tidal volumes of 12 mL/kg, alveolar tidal volume in APRV is minimal, producing the lowest micro-strain and greatest recruitment of all mechanical breath strategies tested.⁸

APRV and Spontaneous Breathing

Spontaneous breathing during APRV has been shown to improve patient comfort, reduce sedation and neuromuscular blocking agent (NMBA) requirements, increase cardiac output and improve renal, gut, brain, and spinal cord perfusion.^{39–46} Although spontaneous breathing is encouraged during APRV, ventilation with up to 30% greater efficiency in CO_2 removal can be achieved in patients that are not spontaneously breathing, such as brain dead patients. In fact, an increase in lung and other organ recovery using APRV has been shown while maintaining effective CO_2 removal despite lower minute ventilation than conventional modes.^{47,48}

Because the CPAP phase during APRV uses an open breathing system allowing active exhalation, spontaneous breathing efforts can occur with as little as 0.2 cmH₂O change (varies depending on manufacturer). Alternatively, closed circuit pressure control modes, typical of IR-PCV, do not permit exhalation unless a patient raises the intra-thoracic pressure threshold and alarm limits are exceeded. This typically causes patient asynchrony, leading to an increase in sedation and possibly addition of NMBAs to control the patient's asynchronous interaction with the ventilator. APRV provides a stable platform in which the CPAP phase occupies approximately 90% of the total cycle time and respiratory dynamics change from active inspiration to active exhalation, unlike conventional ventilation.^{49–51} Therefore, the majority of the patient's spontaneous breathing occurs at a more favorable lung volume, in which the pressure-volume curve is most compliant and the elastic WOB is decreased by maintaining lung volume above FRC.⁵²

Early application of APRV and engaging spontaneous breathing optimizes cardiopulmonary interactions,^{39–46} which may increase patient comfort and venous return. Spontaneous breathing in patients with ARDS receiving low tidal volume (LTV) strategy has been associated with patient-ventilator asynchrony and a worse outcome.⁵³ To date, all studies showing an improved outcome with NMBAs and absence of spontaneous breathing have used LTV strategy with fixed-flow volume ventilation. Conversely, studies with spontaneous breathing in APRV have been associated with attenuation of lung injury and inflammation and improved outcomes.^{7,54} Further, animal studies have shown less inflammation and lung injury in APRV with spontaneous breathing.^{55,56}

The dichotomy of results may be related to key differences when a spontaneous breath is initiated within APRV versus LTV.

Spontaneous breathing in humans is more complex than simply denoting the presence or absence of breathing efforts⁵⁷ and is regulated by multiple controllers, which relay information back to the brainstem to regulate lung volume and inspiratory and expiratory efforts. Spontaneous breathing during APRV results in a significantly different distribution of lung volume, diaphragm position and inspiratory/expiratory muscle activity at the onset of a breath as compared to conventional modes. Patients breathing on APRV typically exhibit a well-described phenomenon known as “defending inspiratory lung volume” by enhancing expiratory muscle activity and inhibiting inspiratory activity, thereby minimizing the possibility of lung overdistension.^{51,58–62} During APRV, the patient maintains a lung volume above FRC and progressively defends the lung volume to keep it within a physiologic normal range by using increasing expiratory muscle tone. Defending the inspiratory lung volume is typically followed by brief relaxations of abdominal muscles, resulting in 30% to 50% passive assist of the inspired tidal volume before diaphragmatic contraction initiates inspiration,⁶² effectively transforming expiration to active and inspiration to passive.

Some ventilators offer the option of adding pressure support (PS) above P_{High} . However, the addition of PS to APRV introduces a triggered, assisted breath, which may partially negate some of the benefits of CPAP breathing.^{43,63} When a PS breath is taken during high lung volume, gas is forced into the lung, overriding the natural protection of the diaphragm's decreased force length ratio as lung volume increases. This results in lung volume above the P_{High} (sum of P_{High} , PS and pleural pressure) and the potential to elevate transpulmonary pressure. This active inspiratory pressure assist above P_{High} is unlike spontaneous breaths taken in APRV without PS, in which active expiratory efforts result in a passive inspiratory assistance when activation of expiratory muscles relax.

EARLY (PREEMPTIVE) APPLICATION OF APRV TO PREVENT ARDS

Preemptive application of APRV has demonstrated a reduction in both incidence and mortality of ARDS.⁶⁴ These clinical observations are further supported by recent laboratory studies using a porcine model of fecal peritonitis and gut ischemia/reperfusion-induced ARDS.^{4,5} These studies demonstrated that APRV applied immediately following this two-hit injury prevented ARDS and distal airspace edema, limited surfactant degradation, reduced lung inflammation, and preserved normal lung architecture as compared with animals receiving conventional mechanical ventilation including the ARDSNet low tidal volume strategy.^{4,5} Nonprotective mechanical ventilation not only induces localized lung inflammation, or bio-trauma, but may also cause downstream inflammation and organ injury.⁶⁵

Alveolar instability, which remains clinically silent, has been shown to be a key mechanism in progressive lung injury

and inflammation, leading to more severe forms of respiratory failure such as ALI and ARDS.^{66–68} Despite decades of trials, treatment of established ARDS is extremely difficult with little change in mortality seen beyond the initial decrease in 1994.^{69,70} Although an initial decrease in mortality was seen with the ARDSNet trial, these results have not been reproduced.^{37,71,72} Even survivors of established ARDS have significant healthcare disabilities including pulmonary and cognitive dysfunction, making it imperative to prevent this syndrome.^{72–75}

SUMMARY

The unique MB_p of APRV with a prolonged CPAP phase and a brief release phase promotes alveolar recruitment and stability while augmenting carbon dioxide (CO₂) clearance. Early application of APRV is a key differentiator among open lung strategies because of the increased patient comfort and ability to engage spontaneous breathing upon restoration of FRC. By altering the cascade of events leading to ARDS and potentially reducing VALI, early application of APRV may be a novel concept to the prevention of ARDS.

A preemptive ventilation strategy applied at the time of intubation should be considered to reduce the incidence of ALI during mechanical ventilation, particularly in patients at high risk such as trauma and surgical patients.^{70,76,77} Since the Emergency Department is the entry point for many patients that require mechanical ventilation, this represents an ideal time to implement protective mechanical ventilation to prevent subsequent ARDS.⁷⁸

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Weaning and Extubation

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INTRODUCTION

Patients require intubation and mechanical ventilation for airway protection, or when a disease process impairs their respiratory capabilities. While most Emergency Medicine (EM) practitioners can easily recognize patients who require intubation, they are often less familiar with the weaning and extubation process.

Weaning is the act of decreasing oxygenation and ventilation support via the mechanical ventilator, and allowing the patient to assume greater control of breathing. *Extubation* is the liberation from mechanical ventilation, and involves the discontinuation of respiratory support and removal of the endotracheal tube. An *unplanned extubation* is defined as an inadvertent removal of the endotracheal tube, either by the patient or practitioner. Studies have shown that up to 48% of patients with an unplanned extubation do not require reintubation.^{1,2} A *failed extubation* is defined as the need for reintubation with 48 to 72 hours, and occurs in up to 30% of patients. Failed extubations can be due to airway pathology, continuation of an extrapulmonary cause of respiratory failure, or the presence of another disease impairing respiration.³⁻⁹ Patients who require early reintubation have an increased risk of mortality, hospital and ICU lengths of stay, and airway complications.^{4,6,7}

Unnecessary delays in weaning and extubation can increase ventilator-associated complications, including pneumonia, barotrauma, and volutrauma.¹⁰⁻¹³ Conversely, premature weaning and extubation carry their own set of complications.^{13,14} Therefore, the clinician must weigh the risks and

benefits of early weaning and extubation versus the potential need for reintubation.

WEANING AND EXTUBATION IN THE EMERGENCY DEPARTMENT

Several studies have cited the increased utilization of the Emergency Department (ED) in recent years,¹⁴⁻¹⁶ as well as an increased number of critically ill patients admitted to the intensive care unit (ICU) from the ED.^{17,18} In addition to the higher volumes and sicker patient population, the length of stay in the ED has also increased.¹⁹

WEANING FROM MECHANICAL VENTILATION

Withdrawing Oxygenation and Ventilation Support

Weaning is the act of decreasing oxygenation and ventilation support via the mechanical ventilator, such that the patient assumes greater control of breathing. There are several well-described modes of weaning and required parameters to facilitate a successful extubation.

Oxygenation can be optimized by increasing the positive end-expiratory pressure (PEEP) and/or the fraction of inspired oxygen (FiO₂) in patients with hypoxic respiratory failure. Briefly, extrinsic, or applied PEEP provides additional pressure above atmospheric pressure to prevent collapse of the

alveoli at end-expiration,²⁵⁻³¹ increasing the functional residual capacity (FRC). PEEP is useful in a variety of disease processes. Excessive PEEP, however, can result in complications, including alveolar injury, lung parenchymal injury, and deleterious cardiovascular effects.^{31,32} The goal, therefore, is to improve alveolar recruitment and arterial oxygenation while using the minimum PEEP settings to avoid these known complications.

Oxygenation can also be improved by increasing the delivered FiO_2 . Excessive oxygen concentrations should be avoided for prolonged periods, as nitrogen washout can occur, exacerbating atelectasis.³³ As with PEEP, the goal is to adjust the FiO_2 delivered to adequately oxygenate the arterial blood, while preventing complications, such as oxygen toxicity. In hypoxic respiratory failure, the most common technique is to start the FiO_2 at 100%, and wean to physiologic levels as the patient's clinical status improves or stabilizes. Clinicians can use pulse oximetry (SpO_2), the percentage oxygen saturation of hemoglobin (SaO_2), and partial pressure of arterial oxygen (PaO_2) levels to guide PEEP and FiO_2 levels.

SpO_2 is a noninvasive method to measure oxygen saturation using dual wavelength spectrophotometry. At a capillary bed, these monitors emit a red light at 660 nm, which is well absorbed by deoxygenated hemoglobin. A second, near-infrared beam is emitted at 940 nm, which is best absorbed by oxygenated hemoglobin. A photodiode detector measures the amount of red and infrared light emitted, and using proprietary software, calculates the SpO_2 , a surrogate of arterial oxygenation. There are several limitations to these devices. For example, a well-vascularized region must be available as an interface, such as a nail bed. Darker nail polish or darker skin pigmentation may affect cause interference of the absorption of the required light wavelengths.^{34,35} Peripheral vasoconstriction, either from shock or the use of vasoactive drugs, limits the use of these devices.^{34,35} Finally, hemoglobinopathies also limit the accuracy of these monitors.^{33,34} In contrast to the SpO_2 , the SaO_2 is calculated from an arterial blood gas sample. Several studies have sited the poor correlation of the SpO_2 and SaO_2 , especially in the critically ill population.³⁶⁻³⁸

The percentage oxygen saturation of hemoglobin (SaO_2), a calculated number, and the partial pressure of arterial oxygen (PaO_2) can both be determined by analyzing an arterial blood gas sample. Based on consensus guidelines, the SaO_2 should be maintained $\geq 90\%$, which correlates to a $\text{PaO}_2 \geq 60$ mmHg, based on the oxygen-dissociation curve of healthy individuals.³⁸ Of course, care must be taken to reassess these parameters in the critically ill or injured, as the oxygen-hemoglobin dissociation curve may be right or left shifted in sick patients, altering both the SaO_2 and PaO_2 values.³⁸

Both the SaO_2 and PaO_2 affect the arterial oxygen content (CaO_2) as follows:

$$\text{CaO}_2 \text{ (mL O}_2\text{/dL)} = [(1.34 \times [\text{Hgb}] \times \text{SaO}_2) + (0.0031 \times \text{PaO}_2)],$$

where 1.34 is the oxygen binding capacity of hemoglobin, and $[\text{Hgb}]$ is the concentration of hemoglobin. To simplify, the

CaO_2 level, which is approximately 20 mL O_2 /dL in healthy patients, is compromised of the component of oxygen bound to hemoglobin, and a smaller contribution of oxygen dissolved in their arterial blood. Once the arterial blood is oxygenated, the oxygen delivery to the tissues can be calculated as follows:

$$\text{DO}_2 \text{ (mL/min)} = Q \times \text{CaO}_2,$$

where Q denotes the cardiac output. Therefore, in addition to titration of the arterial oxygenation, the patient's oxygen carrying capacity, or hemoglobin concentration, and cardiac output must be considered to allow for effective weaning of the patient's oxygen requirement.

As opposed to pure oxygenation abnormalities, some patients require intubation for dysfunction of their ventilation status. *Ventilation* is the movement of air into and out of the lungs. The *minute ventilation* (V_A) is the amount of air that enters the lungs each minute. *Expired minute ventilation* (V_E), is the movement of air out of the lungs per minute, and can be measured as follows:

$$V_E = f \times V_T,$$

where f is the respiratory rate (RR), and V_T is the tidal volume. The total volume of V_A and V_E are not equivalent, as one must account for anatomical and physiologic dead space (V_D). For example, we will assume that the patient is given tidal volume of 500 mL. Approximately 150 mL of this 500 mL V_T remains in the conducting airways, and does not participate in gas exchange. In other words, only 350 mL of the 500 mL V_T , or approximately 2/3 of the inhaled volume, actually reaches the alveoli; the normal ratio of dead space ventilation to tidal volume (V_D/V_T) is ~ 0.25 to 0.35 . However, this ratio can be significantly altered in the critically ill, increasing the mortality of this population, as the percentage of physiologic dead space, or regions of the lung that do not participate in ventilation, is increased.^{39,40} As the alveoli are the sites that participate in gas exchange, the alveolar ventilation (V_A) can also be measured as:

$$V_A = f \times (V_T - V_D).$$

In other words, the true alveolar minute ventilation corrects for the dead space ventilation.

For ventilation to be effective, the body must clear its stores of carbon dioxide (CO_2). The amount of CO_2 in the arteries, or the arterial partial pressure of CO_2 (PaCO_2), can be determined by the following equation:

$$\text{PaCO}_2 = \frac{k \times \text{VCO}_2}{V_A} = \frac{k \times \text{VCO}_2}{V_E \times (1 - V_D/V_T)},$$

where k is a constant, and VCO_2 is the amount of carbon dioxide produced. Based on this equation, the PaCO_2 is proportional to the amount of carbon dioxide produced (VCO_2) and inversely proportional to the amount eliminated (V_E). The production of CO_2 can be increased by a fever, increased metabolism, or an increased work of breathing. CO_2 elimination is affected by drugs, oversedation, fatigue, parenchymal lung disease, and the amount of physiologic dead space. To effectively ventilate, the patient's production of carbon dioxide must match his or her ability to eliminate this toxin.

While normal PaCO_2 ranges from 35 to 45 mmHg, the goal of mechanical ventilation is to alter the expiratory minute ventilation by manipulating the respiratory rate and tidal volume, to correct any acute respiratory acid-base pathology.³⁷ Among patients with acute respiratory distress syndrome (ARDS), the use of lower tidal volume ventilation (6–8 mL/kg) was associated with better clinical outcomes.^{42,43} Improved clinical outcomes were also noted when lower V_T ventilation was used in patients without ARDS.⁴³ While further research is needed, Fuller et al. noted that lower V_T at the initiation of mechanical ventilation may decrease the risk of progression to ARDS.⁴⁴

Physiologic Parameters Necessary for a Successful Weaning Trial

Weaning from mechanical ventilation should begin once the inciting disease process stabilizes or reversible causes are addressed. The goal is to wean the PEEP to between 5 and 8 mmHg and the FiO_2 to $\leq 40\%$ to 50% , while maintaining a $\text{SaO}_2 \geq 90\%$ and a $\text{PaO}_2 \geq 60$ mmHg.^{10,11,38} In addition, the ratio of the PaO_2 to the FiO_2 (P/F ratio) should be > 150 to 200 , to assure resolution of lung injury.³⁶ The patient's minute ventilation (normally 5–6 L/min in healthy patients) can be supported by adjusting the tidal volume and respiratory rate as reversible causes of ventilation deficits are addressed. The goal of ventilatory support is to correct any respiratory acid-base abnormalities, especially the respiratory acidosis caused by excess CO_2 production to a $\text{pH} \geq 7.25$.^{10,11,38}

Once these issues are addressed, the sedation must be minimized to allow the patient to actively participate in the breathing.^{10,11} To successfully extubate, patients must be hemodynamically normal, that is, without ongoing signs of myocardial injury or requiring significant vasopressor support.^{10,11} Consensus guidelines state that the respiratory rate should be less than 35 breaths per minute and the heart rate should be less than 140 beats per minute during a weaning trial for successful extubation.^{10,11} Electrolyte abnormalities and hormonal levels which can affect respiration, such as the phosphate, magnesium, bicarbonate, corticosteroids, and insulin/glucagon level, should also be addressed.^{10,11} Severe anemia, with $\text{Hg} < 7$, should be corrected,^{46,47} as the hemoglobin concentration affects the arterial oxygen content and oxygen delivery. Finally, the patient should ideally be normothermic, as a fever is also associated with delays to extubation.⁴⁸

Once the patient's disease process stabilizes or reverses, these physiologic parameters are met, the patient is able to protect the airway, and the ventilator setting is titrated to minimum levels, the patient can safely undergo a spontaneous breathing trial (SBT) to assess for his or her ability to successfully wean from ventilator support. Evidence from multiple trials demonstrates that a 30-minute SBT, while off sedation, is an effective strategy to predict successful extubation.^{49–55}

Spontaneous Breathing Trials and Different Modes of Weaning

Weaning from ventilatory support via SBTs can be accomplished using various modes, and several studies have been conducted to examine the efficacy of these methods. One possible weaning method is the use of intermittent mandatory ventilation (IMV), in which the clinician sets the T_v , RR, and flow. While mandatory breaths, as dictated by the set respiratory rate, deliver a set tidal volume, spontaneous breaths are not supported by the ventilator, and result in varying tidal volumes depending on patient effort and ability. Several studies noted that IMV was not a superior mode of weaning, as the time to weaning was often greater than other modes.⁵³ This mode was not well tolerated by patients, especially by those with chronic obstructive pulmonary disease (COPD), as the patient often had to generate a greater effort to breathe through a circuit and open the demand valve of the ventilator.^{53–56} Therefore, the consensus guidelines are to avoid IMV as a weaning mode.¹¹

A T-tube, or T-piece, is another method of conducting an SBT. To use a T-piece, the patient is disconnected from the ventilator, and a “T”-shaped tube is connected to the end of the endotracheal tube (ETT) to deliver oxygen. Continuous positive airway pressure, or CPAP, can be added to this circuit, but ventilation is not assisted via this mode. While studies have noted the superiority of the T-piece to weaning using IMV,^{53,54} and the T-tube remains a good weaning method, there are some concerns that the patient is not monitored as closely during this mode, which could be concerning given that the ETT is disconnected from the ventilator.

To counter the work of breathing associated with an ETT,⁵⁷ pressure support ventilation (PSV) has also been examined as a method of weaning from the ventilator. Using the mode, the practitioner can set a level of pressure support, with or without PEEP, and can monitor the T_v , RR, and flow. The level of support is reduced, until just enough to compensate for the ETT and the demand valve of the mechanical ventilator.⁵⁴ This method of weaning has been shown to decrease the workload on the respiratory muscles.⁵⁴ Bouchard et al. argue that PSV weaning results in a lower number of failed extubations, decreased duration of weaning, and decreased length of stay in the ICU.⁵⁴

Some argue that the constant inspiratory pressure delivered by PSV is not physiologic, and should instead be a variable pressure, as it is in nature. To that end, automatic tube compensation (ATC) is a newer mode that helps overcome the work of breathing imposed by the ventilator and ETT in a dynamic way.⁵⁸ While Cohen et al. demonstrated that using ATC can help the patient successfully pass an SBT, there was no significant difference in the failed extubation rates of those who weaned with ATC versus more conventional methods.⁵⁸

Airway pressure release ventilation (ARPV) is another mode of ventilation that can be used during the SBT. The practitioner sets a P_{high} , which is identical to a CPAP level for a predetermined time, or T_{high} .⁵⁹ To augment ventilation, the pressure is dropped to a lower setting, P_{low} , for a short

amount of time, T_{low} .⁵⁹ During the CPAP (P_{high}) and airway release (P_{low}), the patient can spontaneously breathe off sedation, while the ventilator assists with alveolar recruitment and minute ventilation.⁵⁹ To wean from APRV, the P_{high} is gradually lowered and the T_{high} is extended, using the “drop and stretch” technique, until the patient is essentially on CPAP.⁵⁹

The weaning mode chosen by the clinician depends on patient characteristics, as well as physician familiarity. Despite all of the modes available, studies have noted that at times clinicians are overly cautious to begin the weaning process, and unnecessarily delay extubation.^{60,61} In the ICU, daily protocolized weaning trials, and non-physician driven trials can help identify patients who are ready for liberation from the ventilator.^{60,61} Proprietary software is available on some ventilators that allows the machine to adjust the delivered pressure support based on the patient’s respiratory rate, tidal volume, and $PaCO_2$, allowing for automated weaning.⁶²

Weaning Parameters and Preparation for Extubation

To assess the success of an SBT, clinicians obtain parameters, most often at the end of the trial period. One such parameter is the rapid shallow breathing index, or RSBI, which is defined as follows:

$$RSBI = \frac{f}{T_v},$$

where f is the respiratory rate (RR), and T_v is the tidal volume. Patient who fail the SBT tend to have rapid (high RR), shallow (low T_v) breathing, resulting in a higher RSBI. Yang and Tobin noted that patients with an RSBI < 105 breaths/min/L have a 97% sensitivity, 64% specificity of predicting successful extubation.⁶³ Krirger et al. argued that serial RSBI measurement improved the accuracy of predicting extubation success in the elderly population.⁶⁴

The negative inspiratory force (NIF), or maximal inspiratory pressure (MIF), is the amount of force a patient can generate when taking a deep breath, and can be measured pre-extubation. While we often use the cutoff of NIF ≥ -25 mmHg, this test is often a poor predictor of extubation success.^{11,50} The adequacy of ventilation can also be assessed prior to extubation if the patient is able to generate a tidal volume of > 5 mL/kg.¹¹ Finally, the patient should have a vital capacity (VC), the amount of air a patient can exhale after maximum inhalation,¹¹ of > 10 mL/kg.

Final Considerations Prior to Extubation

Once a patient successfully passes the SBT, the clinician must decide if the patient is ready for extubation. Several factors must be taken into consideration, such as the need for further imaging studies or tests, for which the patient would require a protected airway. Frutos-Vivar and colleagues noted that in ICU patients, a positive fluid balance 24 hours prior to extubation and the presence of pneumonia at the time of intubation were factors associated with extubation failure.⁶⁵ A

cuff-leak test can ensure success upon extubation. To perform this maneuver, the ETT cuff is deflated while the patient is still connected to the ventilator, and the difference between the inspiratory T_v and the exhaled volume is measured.⁶⁶ Miller and Cole noted that a cuff leak < 110 mL was highly associated with post-extubation stridor.⁶⁷ The ability to generate an effective cough and clear airway secretions are important for successful extubation, especially in patients with brain injuries or those who cannot follow simple commands.^{45,67-70}

There has been an increased use of noninvasive positive pressure ventilation (NIPPV) immediately post-extubation to decreased the duration of invasive mechanical ventilation, prevent failed extubations, and as a rescue device prior to reintubation, especially among those patients with COPD and neuromuscular disorders.⁷⁰⁻⁷² Ornicco et al. demonstrated the utility of NIPPV in preventing failed extubations in patients who were intubated for acute respiratory distress for at least three days.⁷¹

Finally, prior to extubation, the physician and patient should discuss a possible need for reintubation if there is recurrent respiratory failure. If the patient has a possible need for a reintubate order, the clinician should review the weaning parameters and other factors that can adversely affect extubation, to maximize the possibility of successful liberation from the mechanical ventilator on the first attempt.

EXTUBATION

Patients who pass their SBT are good candidates for extubation, and should be liberated from mechanical ventilation, barring any of the issues discussed earlier. To successfully extubate a patient, the clinician must be prepared for a possible extubation failure, and have the necessary equipment at the bedside in case a reintubation is required.

Prior to extubation, the clinician must arrange for oxygen support post-extubation; most commonly, the patient will be placed on a face-mask, nasal cannula, or humidified oxygen immediately post-extubation. When the oxygen source is ready, the patient should be placed in an upright position while still intubated, and the patient’s oral airway should be suctioned to the posterior pharynx, if possible. The device securing the ETT can be removed. Next, the ETT balloon is fully deflated, which will cause the patient to cough; forewarning the patient that this will occur can ease the anxiety associated with this process. While retracting the ETT, in-line suctioning down the ETT should be performed to remove any tracheal secretions, and to stimulate the cough reflex. Upon removal of the tube, the oxygen source should be placed, at the discretion of the treating clinician. The patient’s lung should be auscultated for any abnormal lower airway sounds, and the neck auscultated for stridor. Finally, the patient should be encouraged to say his or her name, to assess for ability to maintain an airway. The supplemental oxygen source can be further weaned as clinically tolerated, until the patient is tolerating normal respiration on room air, or the patient’s baseline oxygen requirement.

The immediate post-extubation period (up to 72 hours) is a dangerous time for patients who were intubated for respiratory failure.^{3–9} Continued close monitoring of these patients is critical, as post-extubation respiratory distress can be life threatening. Respiratory failure post-extubation can be secondary to upper airway disease, lower respiratory disease, or an extrapulmonary abnormality.^{73–75} Risk factors for failed intubations and the need for reintubation include a prolonged intubation, trauma associated with self-extubation, and overinflation of the ETT cuff.⁷³ Therefore, clinicians should be vigilant for signs of respiratory distress up to 72 hours post-extubation, and reintubate without delay as needed.

SUMMARY

- *Weaning* is the act of decreasing oxygenation and ventilation support via the mechanical ventilator, and allowing the patient to assume greater control of breathing.
- *Extubation* is the liberation from mechanical ventilation, and involves the discontinuation of respiratory support and removal of the endotracheal tube.
- An *unplanned extubation* is defined as an inadvertent removal of the endotracheal tube, either by the patient or practitioner.
- A *failed extubation* is defined as the need for reintubation with 48 to 72 hours.
- Unnecessary delays in weaning and extubation can increase ventilator-associated complications.^{10–13} Conversely, premature weaning and extubation carry their own set of complications.^{13,14}
- Weaning from mechanical ventilation should begin once the inciting disease process stabilizes, or reversible causes are addressed.
- Requirements prior to extubation.^{10,11,36,38,45,67–70}
 - Vital signs—RR < 35 breaths/min, HR < 140 beats/min, normotensive and hemodynamically stable with minimal pressor requirement, normothermia.
 - Oxygenation—PEEP < 8 mmHg, FiO₂ ≤ 40–50%, SaO₂ ≥ 90%, PaO₂ ≥ 60 mmHg, PaO₂/FiO₂ ratio > 150 to 200.
 - Ventilation and pulmonary function—V_T > 5 mL/kg, VC > 10 mL/kg, pH ≥ 7.25, NIF ≥ -25 mmHg.
 - RSBI < 105 breaths/min/L.
 - Hemoglobin > 7 mg/dL.
 - The ability to maintain a patent airway.
 - Cuff-leak test > 110 mL.
 - The ability to generate an effective cough and clear airway secretions.

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Noninvasive Positive Pressure Ventilation

Brian J. Wright • Todd L. Slesinger

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INTRODUCTION

Acute respiratory distress is a frequent problem encountered by emergency physicians and intensivists. Often, the clinician must act to ensure adequate oxygenation and ventilation before a definitive diagnosis is achieved. The treatment of acute respiratory distress requires an aggressive approach that entails use of medications, oxygen, and often positive pressure ventilation. Historically, patients that required positive pressure ventilation underwent endotracheal intubation (ETI) and were placed on a mechanical ventilator. However, over the past two decades, there has been an increased use of noninvasive positive pressure ventilation (NIPPV).^{1,2} As opposed to ETI, NIPPV uses an external mask interface to deliver positive pressure to the patient.

NIPPV and ETI with conventional ventilation are not synonymous alternatives; NIPPV is not warranted when the airway needs to be secured and when higher levels of positive pressure are required. Rather, NIPPV should be considered an additional tool that can augment medical care to possibly prevent ETI. This chapter will discuss the use of NIPPV in the emergency medicine patient with acute respiratory distress.

PHYSIOLOGY OF NIPPV

Nomenclature

There are two major types of NIPPV that are used in the pre-hospital and emergency medicine setting: continuous positive airway pressure (CPAP) and bi-level positive airway pressure (BiPAP).

CPAP is provided throughout the entire respiratory cycle (see Figure 7-1). There are small variations in pressure that are

dependent on patient respiratory effort. The set pressure will very closely approximate mean airway pressure (P_{ma}). The amount of flow or tidal volume (TV) will depend on patient effort, lung compliance and the fit of the mask.

BiPAP consists of two applied pressures: inspiratory positive airway pressure (IPAP) and expiratory positive airway pressure (EPAP) (see Figure 7-2). EPAP is similar to applied positive end expiratory pressure (PEEP) on the mechanical ventilator, maintaining positive pressure throughout the expiratory cycle. IPAP provides a higher positive pressure during inspiration to support the work of breathing and augment ventilation.

CPAP and EPAP: Opening the Lung and Keeping It Open

CPAP and EPAP (in BiPAP) are analogous to applied PEEP in the mechanically ventilated patient, applying pressure above that of atmospheric pressure during the expiratory cycle. The addition of positive pressure during the expiratory cycle can have multiple physiologic effects, and depending on particular patient pathophysiology, these effects can be beneficial or harmful.

The addition of CPAP and EPAP (applied PEEP) are helpful in the treatment of hypoxemic respiratory failure that is refractory to supplemental oxygen. The beneficial effects of applied PEEP in hypoxemic respiratory failure occur primarily through the opening of collapsed, atelectatic, or fluid-filled alveoli that have a low ventilation-to-perfusion ratio (V/Q). In these alveoli, there is absent or inadequate ventilation and blood shunts from the right side of the circulation to left side without unloading carbon dioxide or oxygenating

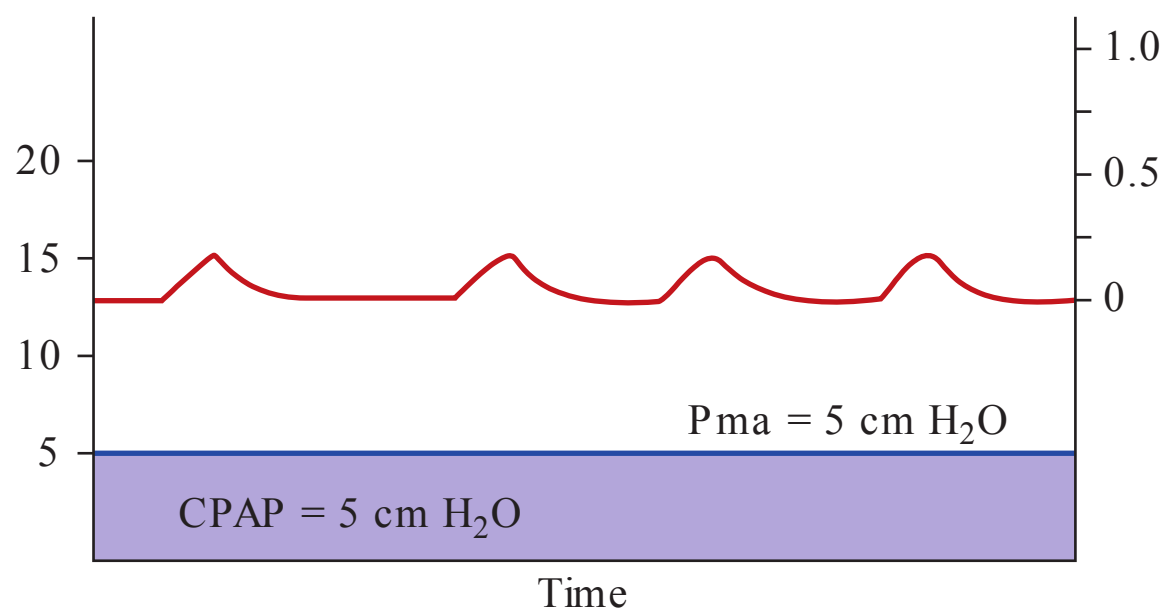


FIGURE 7-1 Continuous Positive Airway Pressure (CPAP). CPAP set at 5. Patient breathing spontaneously, with approximately 200 cc tidal volume (VVT). Mean Airway Pressure (Pma) is approximately 5 cm H₂O. Pressure and TV tracings are ideal.

hemoglobin. Some of these fluid-filled or collapsed alveoli are “recruitable” and have the potential to be “opened” and take part in gas exchange, depending on the underlying disease process and severity of illness. “Recruitable” alveoli can open and close during the respiratory cycle or remain closed throughout the entire cycle. Applied PEEP can help limit expiratory collapse by providing positive pressure during exhalation that splints the alveoli open, or it can serve as a pressure head that opens collapsed alveoli. Opening collapsed alveoli decreases the shunting of venous blood and leads to an improvement of hypoxemia.³⁻⁵

At higher pressures, applied PEEP has negative effects that may outweigh the benefits of recruitment. First, some diseased alveoli are not recruitable and increasing levels of applied PEEP will not improve shunt affect.⁴ Second, high alveolar pressures can cause overdistention of healthy alveoli, leading to barotrauma and the release of inflammatory cytokines, propagating pulmonary and nonpulmonary organ injury.⁴ Third, high PEEP can have negative effects on venous return and cardiac output in preload dependent states (e.g., sepsis, hypovolemic shock), leading to decreased oxygen delivery and tissue perfusion.⁴ Finally, high PEEP can paradoxically worsen V/Q mismatch by overdistending alveoli, decreasing blood flow to previously perfused healthy lung segments and increasing blood flow through the lung shunt.³⁻⁵

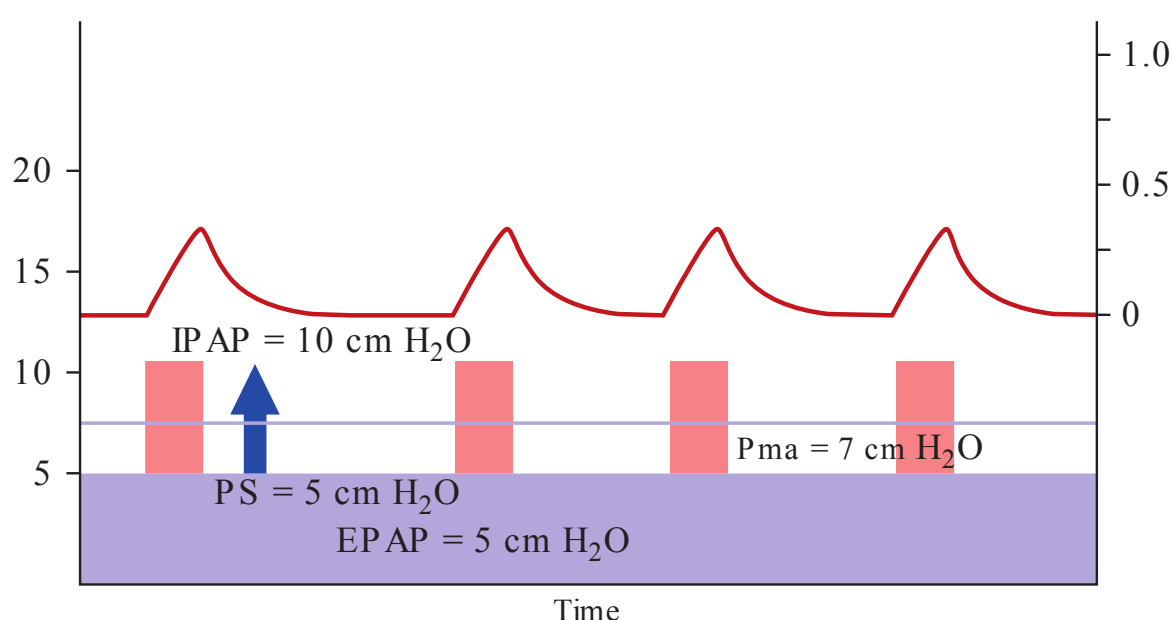


FIGURE 7-2 Bilevel Positive Airway Pressure (BiPAP). Inspiratory Positive Airway Pressure (IPAP) set at 10 cm H₂O. Expiratory Positive Airway Pressure (EPAP) set at 5 cm H₂O. Pressure Support (PS), IPAP-EPAP is 5 cm H₂O. Mean Airway Pressure (Pma) is approximately 7 cm H₂O. Patient breathing spontaneously, TV is approximately 300 cc. Pressure and VTV tracings are ideal.

The level of applied PEEP provided in NIPPV is usually beneficial to patient oxygenation. Provided that the patient is not in a preload dependent state, the negative effects of applied PEEP usually occur at higher pressures that are not well tolerated by patients because of discomfort and air leaks from the mask interface. At higher pressures, gastric distention and aspiration also become a concern. Studies examining bag valve mask ventilation suggest that gastric distention and aspiration is unlikely at pressures below 25 cm H₂O.⁶

If a patient requires higher levels of CPAP or EPAP (greater than 10 or 12 cm H₂O) to maintain oxygenation, this should signal that the clinical status is worsening and that the disease state is not amenable to NIPPV. Conventional ETI with mechanical ventilation should be strongly considered in these situations.

Flow and Tidal Volume: Getting Air In and Out of the Lungs

Airflow and ventilation are directly dependent on the pressure gradient and inversely related to airway resistance from the atmosphere to the alveolus. This can be conceptually explained as Ohm's law:

$$(1) \quad V = IR$$

Rearranging Ohm's law for flow gives you the following:

$$(2) \quad \begin{aligned} \text{Flow} &= \Delta \text{ Pressure} / \text{Resistance} \quad \text{or} \\ \text{Flow} &= (P_{\text{atm}} - P_{\text{alv}}) / R \end{aligned}$$

Airway resistance is important in many different disease states (e.g., chronic obstructive pulmonary disease [COPD] and asthma), and it is essential that the clinician optimize medical treatment (i.e., steroids and β -agonists) to reverse the underlying disease state whenever possible. In the spontaneously breathing individual, the pressure gradient between the alveolus and the atmosphere is accomplished by creating negative pressure in the thorax. At the onset of inspiration, the diaphragm and intercostal muscles contract, increasing intrathoracic volume and decreasing intrathoracic pressure. Relative to the atmosphere, the alveolus is at a negative or lower pressure and air flows through the airways down a pressure gradient into the alveolus. At the end of inspiration, the elastic recoil of the chest wall increases alveolar pressure, creating a positive pressure relative to the atmosphere; air flows out of the lungs down a pressure gradient.^{3,5}

The same principle of air flowing down a pressure gradient applies to noninvasive ventilation and other forms of positive pressure ventilation. In both cases, during inspiration the ventilator provides support in the form of positive pressure at the airway to create a pressure gradient for air to flow from the atmosphere (or ventilator) into the alveolus. Atmospheric pressure is made more positive (as opposed to alveolar pressure becoming more negative) to create the pressure gradient necessary for inspiratory flow to occur. Exhalation is similar to the non-ventilated patient in that it is a passive phenomenon in which the elastic recoil of the chest wall is used to exhale air down a pressure gradient.

Ensuring adequate tidal volume and minute ventilation is necessary for carbon dioxide elimination. Assuming a constant airway resistance, tidal volume is dependent upon the pressure gradient between the alveolus and the atmosphere. Understanding this concept is helpful when manipulating the noninvasive ventilator. Rearranging Equation (2) to noninvasive parameters yields the following:

$$(3) \quad \text{Tidal Volume (TV)} \approx (\text{IPAP} - \text{EPAP})/R$$

TV and flow are dependent on the level of pressure support provided by the BiPAP. Pressure support equals the difference between IPAP and EPAP. Increasing pressure support, provided that the patient has an adequate respiratory rate, will increase TV and minute ventilation and augment ventilation.

If the patient is not improving, or requiring excessive amounts of pressure support to maintain appropriate mental status, pH and PaCO₂, TV and minute ventilation, and comfort level, the trial of NIPPV should be discontinued and the patient should be placed on invasive mechanical ventilation.

SETUP AND PRACTICAL APPLICATIONS

Patient Selection

The appropriate selection of patients with respiratory distress for application of either NIPPV versus ETI and conventional ventilation is critical to minimize additional morbidity and mortality.⁷ First, the patient should have a derangement in pulmonary physiology that requires positive pressure respiratory support. Clinically, the patient should have moderate to severe respiratory distress with evidence of tachypnea, accessory muscle use, or paradoxical abdominal muscle use. This signifies increased work of breathing, and if left unchecked can progress to respiratory failure. Supplemental or laboratory evidence of moderate to severe respiratory distress includes a respiratory acidosis (pH < 7.35 with a PaCO₂ > 45 mmHg) or severe hypoxemia (oxygen saturation < 92% despite supplemental oxygen or a PaO₂/FiO₂ ratio {P/F} < 200), and can also be used to guide the physician in selecting patients for NIPPV. However, the physician should interpret laboratory data appropriately given the clinical scenario: a PaCO₂ of 40 mmHg and oxygen saturation of 92% in an asthmatic can have a significantly different meaning than the same blood gas value in a patient with a COPD or CHF exacerbation. Second, the patient should have a disease process that is amenable to treatment with NIPPV and has a high likelihood of rapid reversibility, for example, exacerbations of COPD or CHF. In these patients, NIPPV should be started as soon as possible to prevent fatigue, further organ dysfunction, and worsening respiratory distress. Recent evidence suggests that NIPPV is most successful when used early and not as a late rescue maneuver.⁸ Finally, contraindications and predictors of failure to NIPPV, such as apnea or respiratory arrest, medical instability, inability to protect airway or manage secretions,

excessive agitation, poor mask fit, or recent upper airway or gastrointestinal surgery should be absent.^{7,9}

An exception to this rule is made for patients who have a Do-Not-Intubate (DNI) order. Acute respiratory distress and failure are often multifactorial, and the emergency medicine clinician is frequently required to treat and stabilize with incomplete patient data. Provided that contraindications are not present, a 1-to 2-hour trial of NIPPV may be warranted if the clinician deems NIPPV appropriate.^{7,9} If there is improvement in the patient's clinical status and blood gas parameters, NIPPV should be continued or weaned if applicable. However, if the patient's status does not improve, deteriorates, or it is determined that the patient has a disease process that is not amenable to NIPPV, the plan of action should be reassessed and therapy should be adjusted. In select patients that are DNI or DNR, palliative care measures should be initiated. A major risk of NIPPV is delaying ETI in patients that require mechanical ventilation, and there is a potential for an increased morbidity and mortality in those patients that linger on NIPPV.⁷⁻¹¹ If there is no improvement after a trial period, or any deterioration, ETI should be conducted to prevent intubation under crash conditions.

Patient and Noninvasive Ventilation Interface

There are three basic interfaces or masks that the clinician can use to provide NIPPV: helmet, nasal mask, and full face mask. Each has its own strengths and weaknesses.

The helmet interface encases the patient's entire head. There is some concern that with the helmet interface patients can rebreathe carbon dioxide, particularly if the ventilator becomes disconnected from the patient.^{7,12} The helmet interface can also be louder than the oral or nasal interface.^{7,12} However, there is less risk of skin breakdown and this interface may be more comfortable for prolonged NIPPV use.^{7,12} The majority of clinical studies did not use a helmet interface, and the experience with this type of interface in U.S. centers is limited.⁷

The nasal mask is a partial mask that goes around the nose of the patient. The patient's mouth is not covered. This type of interface is commonly used in chronic conditions like obstructive sleep apnea. The nasal mask may be more comfortable than the standard full face mask and provokes less claustrophobia. However, it is not particularly suited for the acute setting because of the potential for large air leaks and loss of pressure when the patient opens or breathes through the mouth.^{7,9,12}

The most commonly used interface in the ED and critical care setting is the full face mask.^{7,9,12} The full face mask covers the nasal bridge, goes around the nose, then forms a seal around the chin and mouth. When using the full face mask, it is important to minimize the leak of air around the face mask. An air leak will limit the amount of pressure and volume provided to the patient. Extended use or an overly tight fit can lead to pressure sores on the face. Some patients experience discomfort and a sensation of claustrophobia with the full face mask and positive pressure ventilation.^{7,9,12} It is

often necessary for the clinician to be at the bedside to provide reassurance and make adjustments to the ventilator and face mask. The clinician may decide to provide the patient with analgesia or anxiolysis; however, the negative effects and risks of respiratory and mental status depression must be taken into consideration.

Initial Settings and Patient Monitoring

When choosing initial NIPPV settings, it is important to consider the patient's underlying disease process, the need for positive pressure support, and patient comfort and compliance. Increased patient compliance at lower pressures must be weighed against improved respiratory mechanics, ventilation and oxygenation at higher pressures. A common BiPAP starting point for many emergency medicine physicians is to begin with an IPAP of 10 cm H₂O and an EPAP of 5 cm H₂O—"10 and 5." This is an acceptable starting point as lower initial pressures may help facilitate patient compliance. However, "10 and 5" provides a pressure support of about 5 cm H₂O, slightly less than or equal to the amount of pressure support utilized in weaning trials. There is a subtle yet important difference in nomenclature when describing pressure support in BiPAP and conventional mechanical ventilators. On the BiPAP, "10 and 5" translates to an IPAP of 10 cm H₂O and an EPAP of 5 cm H₂O. The "10 and 5" on the conventional mechanical ventilator utilized during a pressure support wean is actually "10 over 5"—an inspiratory pressure of 15 cm H₂O and expiratory pressure of 5 cm H₂O. It is therefore critical that the clinician monitors response and titrates pressures appropriately to ensure adequate gas exchange and decrease work of breathing. Inadequate pressure support or PEEP (EPAP) may increase work of breathing.^{7,9}

When monitoring patients on NIPPV it is important to look for certain subjective and objective criteria (see Table 7-1). First, examine the patient ventilator interface for air leaks. Air leaks may be audible. You can also place your hands around the mask to feel for air leaking. Air leaks decrease the amount of support provided to the patient and can lead to NIPPV failure. One method to compensate for air leaks is to increase the applied pressures to increase the actual support that the patient receives. However, increasing the applied pressures can lead to increased air leak. The best way to overcome air leaks is to readjust the mask or change to a different interface. Second, the clinician should look at clinical parameters, such as the patient's mental status, use of accessory muscles, comfort level, and presence of subjective dyspnea or chest pain. Worsening mental status can imply a worsening respiratory status, worsening PaCO₂, and an increased risk of aspiration, and should signal the end of the NIPPV trial. The patient should report an improvement in dyspnea, and the clinician should look for decreased accessory muscle use and good patient and NIPPV synchrony. Third, objective clinical data, such as TV on the NIPPV, respiratory rate (RR), heart rate (HR), oxygen saturation (SaO₂) and blood pressure (BP) should be monitored continuously, and



TABLE 7-1: NIV Monitoring

Subjective

- Dyspnea
- Mental status
- Airway maintenance
- Patient comfort
- Patient-ventilator synchrony
- Accessory muscle use
- Air leak

Objective

- Heart rate
- Oxygen saturation
- Blood pressure
- Respiratory rate
- Tidal volume (6–8 cm³/kg)
- ABG: pH, PaCO₂, PaO₂ (baseline and at 1–2 hours)

a baseline arterial blood gas (ABG) and 1-to 2-hour ABG should be obtained to measure pH, PaCO₂ and PaO₂.

Clinical Example: Ventilation and Work of Breathing

To give a clinical example, a patient is placed on BiPAP for hypercarbic respiratory failure secondary to a COPD exacerbation. This particular patient has inadequate ventilation, respiratory acidosis, and elevated work of breathing. The clinician selects a standard setting of IPAP 10 cm H₂O and EPAP 5 cm H₂O, adjusting the FiO₂ to maintain oxygen saturation between 88% to 92%. Additional oxygen saturation is not required, and can run the risk of inhibiting respiratory drive. An EPAP of 5 cm H₂O is a good starting point to overcome intrinsic PEEP and the inspiratory threshold to decrease the work of breathing. An IPAP of 10 cm H₂O provides a pressure support of 5 cm H₂O. This is minimal, but patient compliance is a concern so the clinician begins with lower pressures.

After a trial period, the clinician finds that the patient is not pulling enough TV on the BiPAP and the PaCO₂ level is not dropping appropriately. A decision is made to continue the BiPAP and increase pressure support. Rather than increase both the IPAP and EPAP together, the clinician should only increase the IPAP (see Figure 7-3). Increasing the IPAP and EPAP equally together will maintain the same pressure gradient between the alveolus and the ventilator and the same TV and ventilation. By selectively increasing the IPAP, the clinician increases the pressure gradient between the atmosphere and ventilator, therefore will increase the flow of air and TV.

Clinical Example: Hypoxemia

In the second clinical example, a patient with a CHF exacerbation and hypoxic respiratory failure is placed on BiPAP. Again the clinician selects a standard setting of IPAP 10 cm H₂O over EPAP of 5 cm H₂O, and applies supplemental

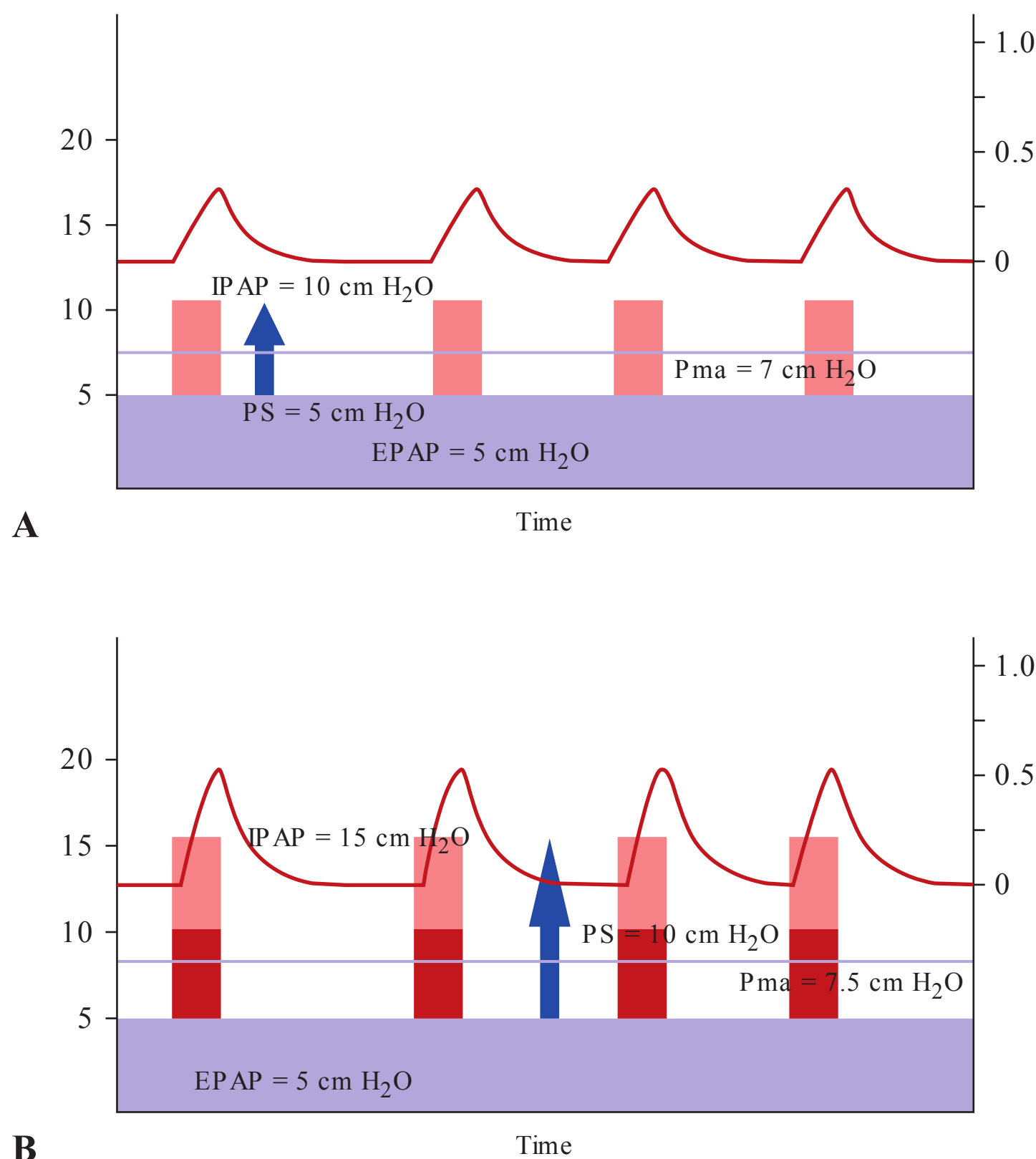


FIGURE 7-3 A and B. Ventilation and Pressure Support. Pressure and Vt tracings are ideal. **A.** Patient placed on BiPAP of 10 and 5, corresponding to IPAP of 10 cm H₂O and EPAP 5 cm H₂O. Patient pulling minimal TV because pressure support (PS) is only 5 cm H₂O. **B.** To increase PS, IPAP is increased to 15 cm H₂O and EPAP is kept same. PS is now 10 cm H₂O and patient's TV has improved. Mean Airway Pressure (Pma) has increased minimally.

FiO₂. Initially, the clinician will increase the level of FiO₂. Unfortunately, 100% FiO₂ is often not sufficient to improve hypoxia. If the patient doesn't adequately improve, the clinician must improve Pma (see Equation (5)) and alveolar recruitment to improve V/Q mismatch, reduce shunt and effectively treat hypoxia.

$$(5) \quad \text{Mean Airway Pressure (Pma)} \\ \approx (p_1 t_1 + p_2 t_2 + \dots p_n t_n) / \text{time} \quad (14)$$

This is best accomplished by increasing the EPAP (or PEEP) level of support as this will have a greater impact on the mean airway pressure than increasing pressure support. IPAP and EPAP are both increased equally together (see Figure 7-4). This will provide the same level of inspiratory support while increasing Pma and oxygenation.

Understanding Failure and Not Letting Patients Linger on NIPPV

NIPPV is one of the most well-studied interventions in critical care medicine and one of the handful of treatment modalities associated with mortality benefit. Landoni et al¹⁵ examined all published trials in critical care that showed mortality benefit. NIPPV had the most robust evidence base with eight multicenter randomized controlled trials showing a statistically significant survival improvement in patients affected by acute respiratory failure.¹⁵ This effect has been shown over a variety of clinical contexts but was dependent on the presence of COPD patients in the study population. Unsuccessful

NIPPV has been shown to be independently associated with death in patients with acute respiratory failure.¹⁰ Failure to recognize NIPPV failure and inappropriate patient selection can both delay invasive mechanical ventilation and lead to worse outcomes. Therefore it is important for clinicians who use NIPPV to recognize the clinical signs that predict NIPPV failure in order to avoid intubation under crash conditions and increased morbidity and mortality. NIPPV failure has been defined according to three different temporal moments: immediate (less than 1 hour); early failure (1 to 48 hours); and late failure (after 48 hours).¹¹

Excluding patients that were inappropriately selected for NIPPV, immediate NIPPV accounts for 15% of cases of failure.¹¹ Common causes of immediate failure were: weak cough reflex and/or excessive secretions, hypercapnic encephalopathy and coma, intolerance and psychomotor agitation, and patient-ventilator asynchrony.¹¹ Suggested interventions include: aggressive chest physiotherapy and appropriate early fiberoptic bronchoscopy, minimizing FiO₂ and setting a backup rate to prevent hypoventilation, judicious use of sedation (agents that do not suppress respiratory drive such as ketamine and dexmedetomidine may be preferred), and minimize air leaks and adjust NIPPV settings to minimize work of breathing.

Early failure accounts for approximately 65% of NIPPV failure. In addition to the suggested NIPPV interventions for immediate failure, aggressive management of the underlying disease that caused acute respiratory failure is important to minimize early failure. Predictors of early failure:

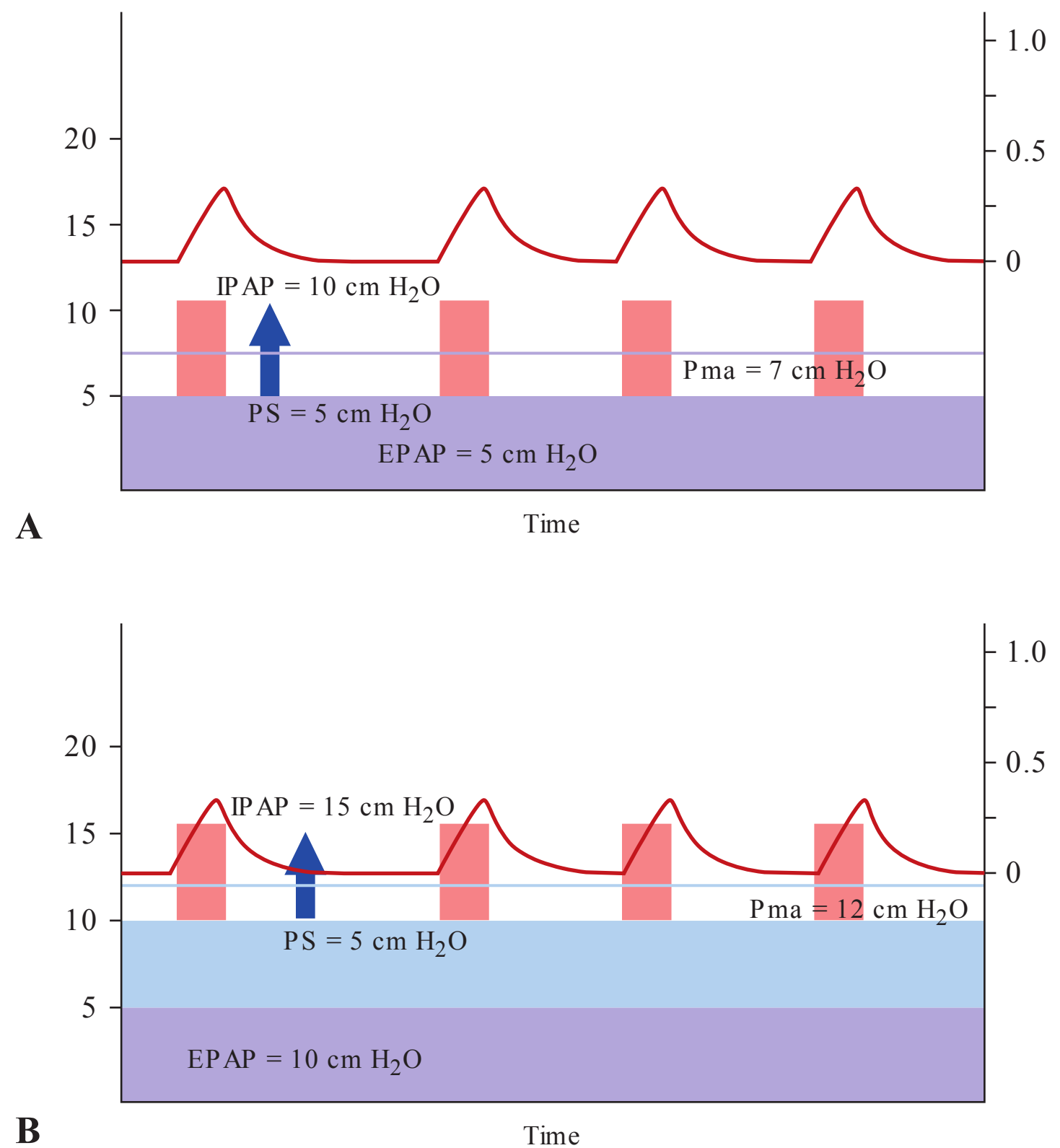


FIGURE 7-4 A and B. Oxygenation and Mean Airway Pressure. Pressure and Vt tracings are ideal. **A.** Patient placed on BiPAP of 10 and 5, corresponding to IPAP of 10 cm H₂O and EPAP 5 cm H₂O. However, patient is still hypoxic on 100% FiO₂. **B.** To increase Mean Airway Pressure (Pma), IPAP and EPAP are increased together to IPAP of 15 cmH₂O and EPAP of 10 cm H₂O. Pma increases from 7 cm to 12 cm H₂O. PS remains at 5 cm H₂O and TV stays the same.

inability to correct gas exchange ($\text{PaO}_2/\text{FiO}_2$ ratio ≤ 146 at 1 hour or $\text{pH} < 7.25$), metabolic acidosis, shock and multiorgan failure, diagnosis of acute respiratory distress syndrome (ARDS) with moderate hypoxemia ($\text{PaO}_2/\text{FiO}_2$ ratio < 200), pneumonia or septic shock, and an increased respiratory rate (> 25 breaths/min in hypoxemic respiratory failure, and > 30 for hypercapneic respiratory failure).¹¹ An increase in time to correct gas exchange, improve respiratory rate, and correct organ dysfunction is associated with worse outcomes.¹¹

Late NIPPV failure accounts for approximately 15% of NIPPV failures.¹¹ Disturbances of sleep, severity of acute or chronic illnesses, inadequate nutrition and hyperglycemia have been associated with late failure.¹¹ Again, it must be emphasized that it is important for clinicians to select the appropriate patients for NIPPV, recognize the clinical signs that will predict NIPPV failure, escalate care early and appropriately in patients that fail NIPPV, and avoid intubation under crash conditions to prevent an increased morbidity and mortality.

CLINICAL SCENARIOS AND EVIDENCE BEHIND NIPPV USE

Before examining the studies of NIPPV use, it is important to discuss their validity and application to bedside care. The respective studies, in addition to being conducted in centers with extensive experience with NIPPV, had strict inclusion and exclusion criteria. The majority of studies excluded patients with hemodynamic instability, multiorgan dysfunc-

tion, altered mental status, difficulty in maintaining their airway, or excessive secretions. In addition, the sickest patients were intubated before randomization, and were not included. NIPPV is appropriate for only a select subgroup of patients with acute respiratory distress.

COPD and Hypercarbic Respiratory Failure

The use of NIPPV in acute COPD exacerbations and hypercarbic respiratory failure is well supported by multiple clinical trials.¹⁶⁻¹⁹ NIPPV is believed to help improve respiratory mechanics and symptoms in patients with COPD exacerbations through a number of mechanisms. First, by providing pressure support, BiPAP can partially offload the work of breathing of the diaphragm and other respiratory muscles. Second, providing extrinsic PEEP in certain scenarios may reduce air trapping and dynamic hyperinflation and overcome intrinsic PEEP, leading to improved pulmonary function. Finally, NIPPV can decrease the cost of breathing. Normal breathing utilizes approximately 2% of cardiac output; this can increase to 20% in patients with acute respiratory distress. By improving PaCO_2 and pH, NIPPV can improve mental status and respiratory muscle function, improving the efficiency of breathing.⁴

The use of NIPPV in COPD, as in other disease states, is intended to bridge the patient through the exacerbation until medical therapy can ameliorate and reverse the disease process. For the appropriately selected patient without

exclusion criteria, NIPPV should be considered to be first-line therapy for COPD exacerbations. NIPPV success rates have been cited near 80% to 85%.¹⁶ The beneficial effects of NIPPV can be attributed to decreasing the complications associated with ETI and conventional mechanical ventilation (e.g., over sedation, ICU-associated weakness, ventilator-associated pneumonia (VAP), and pneumothorax).^{7,9,16–19} In addition, patients on NIPPV “wean” faster than patients on standard mechanical ventilation.^{7,9,16–19}

In 1995, Brochard et al.¹⁷ published the results of a randomized multicenter trial on the use of NIPPV in patients with acute exacerbations of chronic obstructive pulmonary disease. In this study, the authors compared standard medical therapy alone to a combination of standard medical therapy and NIPPV in 85 patients with an acute exacerbation of COPD. The NIPPV group had a lower rate of endotracheal intubation (26% vs. 74%, $p < .001$), frequency of complications (16% vs. 48%, $p < .001$), hospital length of stay (23 ± 17 days vs. 35 ± 33 days, $p = .005$), and in-hospital mortality (9% vs. 29%, $p = .02$). Importantly, the sickest patients (approximately 30%), who required emergent intubation or were hemodynamically unstable were *excluded* from the trial. This study was conducted in an ICU setting.

In 2000, Plant et al.¹⁸ conducted a similar but larger multicenter trial on the use of NIPPV in acute exacerbations of COPD. The authors included patients with COPD exacerbations that had tachypnea, hypercarbia, and mild to moderate acidosis (defined as pH 7.25 to 7.35). This study differed from the earlier study by Brochard¹⁷ in that it was conducted in a general respiratory ward and not in an ICU—still not a busy emergency department (ED) but in theory closer to the functioning and staffing of the ED than an ICU. Plant¹⁸ found similar results to the prior work of Brochard.¹⁷ In 236 randomized patients, NIPPV was associated with a reduced need for intubation (15% vs. 27%, $p = .02$), lower in-hospital mortality (10% vs. 20%, $p = .05$) and a more rapid improvement in breathlessness and respiratory rate.¹⁸

In general, the beneficial results demonstrated by Brochard and Plant have been reproduced in multiple studies examining the use of NIPPV in acute COPD exacerbations. In 2001 and then again in 2004, Ram et al.¹⁹ conducted a systematic review of the literature for the *Cochrane Database* on the use of NIPPV in acute COPD exacerbations. In a pooled analysis, the use of NIPPV was associated with decreased mortality (RR 0.52; 95% CI 0.35 to 0.76), decreased need for intubation (RR 0.41; 95% CI 0.33 to 0.53), reduction in treatment failure (RR 0.48; 95% CI 0.37 to 0.63), less complications with associated treatment (RR 0.38; 95% CI 0.24 to 0.60), and shorter length of stay (LOS) (Weighted Mean Difference (WMD) - 3.24 days; 95% CI - 4.42 to - 2.06). In addition, NIPPV showed beneficial effects on physiologic respiratory parameters such as pH, PaCO_2 , and respiratory rate. They concluded that data from good quality randomized controlled trials (RCT) supports the benefit of NIPPV as first line therapy in conjunction with medical care in suitable patients with respiratory failure secondary to an acute exacerbation of COPD.

In addition they further recommend that NIPPV should be considered early in the course of respiratory failure, before severe acidosis ensues, as a means of reducing the likelihood of ETI, treatment failure and mortality.¹⁵ These results were confirmed by Cabrini et al.⁸ In their review of all randomized controlled trials of noninvasive ventilation in acute care settings, use of NIPPV in COPD was associated with a lower risk of mortality (RR 0.56, 95% CI 0.42, 0.74) with a NNT of 11.

The use of NIPPV in hypercarbic narcosis is controversial. Altered mental status has classically been an exclusion criteria or contraindication to the use of NIPPV. However, two studies suggest that NIPPV may be effective in patients with encephalopathy secondary to hypercarbic respiratory failure. Diaz et al.²⁰ conducted a prospective observational study comparing the use of NIPPV in patients with acute hypercarbic respiratory failure and a Glasgow Coma Scale (GCS) ≤ 8 ($n = 76$) versus those with a GCS > 8 ($n = 605$). Their group found similar results between the two groups with regards to in hospital mortality (33.2% in “No Coma” groups vs. 26.3% in “Coma” group, $p = 0.17$) and success with avoidance of endotracheal intubation (70.1% in “No Coma” group vs. 80% in “Coma” group, $p = 0.04$). In the subgroup with COPD, the results were even more encouraging with 89% of patients without coma avoiding intubation and 86.3% of patients with coma avoiding intubation.

Improvement of GCS within 1 hour of therapy predicted NIPPV success (OR 2.32, 95% CI 1.53–3.53), again highlighting the need for the clinician to *reassess* the patient’s response to NIPPV, search for objective criteria of success or failure, and appropriately escalate therapy if necessary. The major weakness of the Diaz study is the lack of a control group, but the results suggest that a trial of NIPPV may be warranted in patients with hypercarbic narcosis and especially in COPD patients with hypercarbic narcosis. There was only one episode of aspiration pneumonia in 76 patients. Scala et al.²¹ conducted a case controlled study of 80 individuals, matching comatose and non-comatose COPD patients. They found similar results to Diaz’s group. However, patients with worsening mental status depression had higher failure rates and higher mortality than matched controls with normal mental status. There were no cases of aspiration in the selected patients. Patients who improved usually did so within the first hour, and the majority of cases of NIPPV failure were secondary to hemodynamic instability and need for vasopressors. Again the authors suggest that a trial of NIPPV may be warranted in patients with hypercarbic narcosis.

The most recent Global Initiative for Chronic Obstructive Lung Disease (GOLD) in 2015 recommends NIPPV for use in COPD exacerbations in patients with moderate to severe disease, defined by dyspnea with clinical signs suggestive of respiratory muscle fatigue respiratory acidosis ($\text{pH} \leq 7.3$) or hypercapnea ($\text{pCO}_2 > 45$).¹⁶ NIPPV in multiple clinical trials has consistently improved respiratory acidosis and decreased respiratory rate, sensation of breathlessness, hospital LOS, complication rate, need for intubation, and mortality. NIPPV should be considered in patients with moderate to severe

dyspnea from a COPD exacerbation who do not require immediate intubation. It is probably prudent to institute NIPPV as early as possible in the disease course.⁸ An altered level of consciousness is usually a contraindication to NIPPV, however if the depressed mental status is secondary to CO₂ retention, the clinician can consider a trial of NIPPV. The patient should be closely monitored for evidence of hemodynamic instability, worsening mental status, respiratory failure, apnea, and aspiration. If the patient does not improve clinically within 1 to 2 hours, therapy should be escalated.

Acute Cardiogenic Pulmonary Edema

The use of NIPPV and CPAP in patients with respiratory distress secondary to acute cardiogenic pulmonary edema (ACPE) is generally well supported in the literature. BiPAP and CPAP are thought to benefit in ACPE by decreasing both preload and afterload, reducing the sensation of breathlessness, decreasing CO₂ retention when present, and, when BiPAP is used, decreasing the work of breathing.⁴ The application of external PEEP increases intrathoracic pressure. This increase in intrathoracic pressure is believed to decrease venous return to right side of the heart, dropping preload and placing the heart on a more favorable part of the Starling curve. Venous return and cardiac output over any given time period are equivalent. In preload responsive states, this drop in venous return is more pronounced, leading to a potentially dangerous drop in cardiac output, blood pressure, and tissue perfusion. In conditions where the heart is adequately fluid resuscitated or volume overloaded (e.g., ACPE) this drop in cardiac output is negligible.⁴

The application of PEEP, via BiPAP or CPAP, is also believed to be beneficial in patients with ACPE through a reduction in afterload. Afterload is the force opposing ventricular contraction. This force is determined by two major variables: systemic arterial resistance and the left ventricular transmural pressure. The left ventricular transmural pressure is equal to the difference between the systolic blood pressure and the intrathoracic pressure.⁴ In patients with ACPE, the clinician administers nitrates and vasodilators, decreasing afterload by reducing systemic arterial resistance and also reducing transmural pressure by reducing systolic blood pressure. The application of PEEP through BiPAP or CPAP raises intrathoracic pressure that leads to a decrease in left ventricular transmural pressure and left ventricular afterload, leading to a decrease in edema formation in the lungs and a decrease in myocardial work.⁴ Numerous studies have compared the use of BiPAP and CPAP in ACPE, with mixed results.

In 2013, Vital et al.²² published a systematic review in the Cochrane database examining the use of BiPAP or CPAP in ACPE. They included a total of 32 trials with 2916 patients. Their results suggest that BiPAP or CPAP significantly reduced hospital mortality (RR 0.66, 95% CI 0.48 to 0.89) and endotracheal intubation (RR 0.52, 95% CI 0.36 to 0.75). The number needed to treat (NNT) to prevent one death was 13 and to prevent one intubation was 8. ICU length of stay was reduced by 1 day. No significant increases in acute

myocardial infarction with BiPAP during (RR 1.24, 95% CI 0.79 to 1.95) or after (RR 0.70, 95% CI 0.11 to 4.26) its application were observed. They concluded that it is effective and safe, but that further large-scale trials are needed.

The validity of the systematic review in critical care medicine has recently been called into question.²³ Lumping together populations from multiple studies will increase the sample size, tighten the confidence interval, and decrease the chance of random error, but unfortunately these populations are often heterogeneous. Analyzing heterogeneous study populations together can serve to amplify systematic errors, threatening accuracy or usefulness of the evidence for the clinician at the patient's bedside.²³ Furthermore, meta-analyses fail to predict the outcomes of future large multicenter randomized trials 35% of the time.²⁴

In 2008, Gray et al.²⁵ published the Three Interventions in Cardiogenic Pulmonary Oedema (3CPO) trial, examining NIPPV in cardiogenic pulmonary edema. This trial was a large, randomized multicenter trial involving 1069 emergency department patients with ACPE. Patients were randomized to standard care (supplemental oxygen), versus CPAP or BiPAP. The 3CPO trial found that CPAP and BiPAP were better than standard care in relieving dyspnea, improving heart rate, respiratory rate, hypercapnea, and acidosis at 1 hour. Unfortunately, these benefits did not translate into a lower hospital mortality rate (9.8% v 9.5%, $p = 0.87$) or intubation rate (2.8% v 2.9%, $p = 0.90$). CPAP and BiPAP were equally effective, and there was no associated increase in the incidence of acute myocardial infarction with BiPAP (27.2% v 26.8%, $p = 0.90$). The authors recommend that NIPPV be used as an adjunctive therapy in patients with ACPE with severe respiratory distress or in patients that do not improve with standard pharmacologic therapy (nitrates, diuretics, and possibly afterload reducing agents).

There are some important critical elements and controversies to point out about the 3CPO trial. First, the sickest patients, those that required immediate life saving interventions (i.e. intubation), were excluded. This exclusion possibly selected a "healthier" group of patients. The intubation rate in the 3CPO trial was approximately 3%.²⁵ In all other trials besides 3CPO, the intubation rate was around 27% in the control groups.^{19,26} It is harder to find a difference in outcomes (i.e. intubation and mortality) when these outcomes are rare to begin with.

Second, this trial was conducted as an open trial with an "intention to treat" analysis. Briefly, intention to treat means that regardless of the actual treatment given, a particular patient is analyzed in the group to which he or she is randomized. With regards to this trial, if a patient was randomized to receive standard care, but shortly after randomization was deemed to need additional support and crossed over to a NIPPV arm, he or she was still analyzed in the standard care arm (and vice versa).

From a research standpoint, the intention to treat study design is critical to protect the randomization process but from a practical standpoint it can make the results difficult to interpret and apply at the patient's bedside. Researchers attempt

to minimize confounding results from crossover among treatment groups. This is not always practically or ethically possible. In the 3CPO trial, between 15% to 24% of patients did not complete the trial in the group they were randomly assigned.²⁵ This high rate of crossover serves as a confounding variable because some patients treated with standard medical treatment likely benefited from NIPPV application, yet were analyzed as successes in the standard treatment group. Approximately 15.5% of the patients treated with standard therapy were put on NIPPV because of worsening respiratory distress or deterioration in blood gas values.²⁵ Similarly, 5.2% to 8.4% of patients treated with NIPPV did not complete the trial because of discomfort with the mask and ventilator.²⁵ A major determinant of NIPPV success or failure is patient compliance and tolerance of treatment.

The aggregated data on the use of NIPPV in ACPE suggests that there is a definite benefit in terms of physiological and clinical parameters. This seems to support its use in the care of patients with ACPE. However, this does not necessarily translate statistically into a reduction in mortality and the reduced need for intubation. Weng et al.²⁶ conducted another systematic review and included the data of the 3CPO trial investigators. They concluded that even with the equivocal results of the 3CPO trial, the previous assessments that the use of CPAP reduces mortality and intubation rates in patients with ACPE, and that BiPAP reduces the need for intubation compared with standard therapy still appear to be true.

Perhaps the most useful information from this, at times, conflicting data is that the use of NIPPV in ACPE does not cause harm. One of the first studies published by Mehta et al.²⁷ in 1997 found an increase rate of myocardial infarction in the BiPAP group (71%) when compared to the CPAP group (31%), leading to an early termination of their study. However, the patients in the BiPAP group had a higher percentage of chest and jaw pain, and likely presented with myocardial infarction rather than developing one on BiPAP. In addition, this study had a small sample size. The 3CPO trial²⁵ and multiple systematic reviews^{22,26} did not find an increased incidence of myocardial infarction with the use of NIPPV, particularly BiPAP.

The question of whether to use CPAP versus BiPAP in ACPE is controversial. From a purely statistical standpoint, it would appear that CPAP has a slight advantage. From Vital²² and Weng,²⁶ CPAP was associated with a statistically significant decrease in hospital mortality and reduced need for intubation. BiPAP was associated with a less robust decrease in mortality and intubation.^{19,26} From a physiological standpoint, BiPAP would seem to be more logical. BiPAP provides all the benefits of CPAP as the EPAP is essentially the same as CPAP. Plus BiPAP better offloads the respiratory muscles and work of breathing, better augments ventilation and improves hypercarbia and respiratory acidosis when present, and better improves dyspnea, heart rate, hypoxemia, and respiratory rate.^{19,25} When compared directly to one another, CPAP and BiPAP perform identically in terms of mortality and need for intubation.^{25,28} The difference appears to be statistical rather

than actual. For ACPE, the use of CPAP and BiPAP appear to be equally effective. However, patients with co-existing COPD or any degree of hypercapnea or respiratory acidosis may benefit more from BiPAP over CPAP.

NIPPV, in addition to aggressive medical management, should be considered *first line* therapy for the appropriately selected patient with ACPE. NIPPV should be avoided in patients who are hypotensive, in shock, or otherwise hemodynamically unstable unless they have a DNI. In addition active ischemia, STEMI requiring emergent intervention, or an unstable arrhythmia should not be present. These patients are better managed by ETI and mechanical ventilation. The BiPAP should be set with an emphasis on a higher EPAP to increase mean airway pressure and lung recruitment that can be used to improve oxygenation, along with supplemental oxygen. Alternatively, CPAP can be used alone. Pressure support, if used, should be adjusted by raising the IPAP to decrease the work of breathing, improve ventilation, hypercapnea and respiratory acidosis as needed. As with all patients on NIPPV, they should be monitored closely for signs of treatment failure, and the clinician should be prepared to escalate care and perform ETI if necessary. Objective data from ABG's, and other clinical parameters like heart rate, respiratory rate, oxygen saturation and dyspnea should be frequently reassessed. After 1 to 2 hours of NIPPV, clinical improvement should be evident. If there is no improvement, or deterioration occurs at any time, intubation should strongly be considered.

The Immunocompromised Patient

ETI and conventional mechanical ventilation are associated with a risk of VAP and other nosocomial infections. VAP can have a 20% to 50% mortality rate.²⁹ NIPPV has been shown to benefit immunocompromised patients by reducing mortality, mainly secondary to prevention of VAP and other nosocomial infections and complications such as pneumothorax.

In a case controlled study looking at NIPPV in 48 acquired immunodeficiency syndrome (AIDS) patients admitted to the ICU with acute respiratory failure secondary to *pneumocystis carinii pneumonia* (PCP), Confalonieri et al.³⁰ showed a decrease in ICU mortality in patients treated with NIPPV (75% v 38%), a reduction in the need for intubation in the NIPPV group (67% avoided intubation), and a decreased ICU LOS (7 ± 4 v 10 ± 4 days) as compared to controls that were intubated on presentation of acute respiratory failure. The retrospective nature of the study makes it difficult to draw complete conclusions. It is very possible that those initially intubated were sicker and destined to do worse, but the fact that intubation was prevented in approximately two-thirds of the patients treated with NIPPV suggests that a trial of NIPPV *is warranted* in AIDS patients with acute respiratory failure secondary to PCP pneumonia.

Hilbert et al.³¹ compared NIPPV with standard treatment (supplemental oxygen) in 52 immunocompromised patients with acute hypoxic respiratory failure, pulmonary infiltrates and fever. They found a decrease in the need for intubation (12 v 20 , $p = 0.03$), fewer serious complications (13 v 21 ,

$p = 0.02$), fewer ICU deaths (10 v 18, $p = 0.03$), and fewer hospital deaths (13 v 21, $p = 0.02$). Again, it is important to emphasize that this study did not compare NIPPV versus intubation, but rather NIPPV versus standard oxygen therapy. The benefits of NIPPV may be most pronounced when used early in the disease process. All of the patients that were intubated died, regardless of initial treatment, highlighting the severity of underlying illness and poor prognosis associated with respiratory failure in the immunocompromised population. Similar results were found by Antonelli et al.³² in immunocompromised patients with acute respiratory failure after solid organ transplantation. In 51 patients with acute respiratory failure after solid organ transplantation, the use of NIPPV was associated with a significant reduction in the rate of ETI (20% v 70%, $p = .002$), a lower rate of fatal complications (20% v 50%, $p = .05$), decreased LOS in the intensive care unit by survivors (mean [SD] days, 5.5 [3] v 9 [4], $p = .03$), and lower intensive care unit mortality (20% v 50%, $p = .05$). An initial trial of NIPPV *is warranted* in immunocompromised patients with acute respiratory failure as it may prevent endotracheal intubation and the complications associated with standard mechanical ventilation, including a high rate of mortality.

Asthma

Clinicians can consider the use of NIPPV for the treatment of acute asthma exacerbations. However, the evidence behind the use of NIPPV for acute asthma exacerbations is not as strong as other disease states like COPD or ACPE. Asthma induced acute respiratory failure is secondary to airflow obstruction and dynamic hyperinflation leading to increased intrinsic PEEP and an increased work of breathing. An early study by Meduri et al.³³ studied the use of NIPPV in 17 patients with status asthmaticus admitted to the intensive care unit, and showed that NIPPV improved clinical and physiologic parameters such as pH, $p\text{CO}_2$, and RR. Only 2 of the patients required intubation. This was a case series and was therefore unable to show if NIPPV can prevent intubation. However, it did demonstrate that a trial of noninvasive ventilation may be safe in status asthmaticus. In a study conducted in an emergency department, Soroksky et al.³⁴ compared BiPAP versus medical therapy alone in 30 patients with severe asthma exacerbations. They found a reduction in the need for hospital admission, more rapid improvement in FEV_1 , and a greater percentage of patients who improved their FEV_1 to greater than 50%. This study was mainly limited by size, and only patients with moderate to severe disease were included. It is difficult to apply this data to status asthmaticus patients with acute respiratory failure because there were no intubations or morbidity in either group. Except for FEV_1 and PEF, other clinically important variables like ICU admission and ICU LOS were not commented on. However, applying NIPPV *early* as opposed to waiting for ICU admission in status asthmaticus patients may explain the very positive results of this trial.

More recently, Gupta et al.³⁵ examined NIPPV in patients with severe acute asthma versus standard-medical-

therapy. In this trial of 53 patients, they found no difference in mortality between the groups. There was similarly no difference in the need for intubation. Of 28 patients in the NIPPV group, only 2 required intubation, whereas none of the 25 patients in the control arm required intubation (RR 4.48, 95% CI 0.23, 89.13). NIPPV, however, was associated with a significantly shorter ICU and hospital length of stay. Four patients in the control arm required rescue therapy with NIPPV.

A Cochrane meta-analysis by Ram et al.³⁶ and then Lim et al. in 2012,³⁷ found the use of NIPPV in asthma exacerbations to be “promising” but also still “controversial” because of lack of evidence. More evidence is needed to develop evidenced-based recommendations, but it is generally agreed that a trial of NIPPV is warranted in select patients with severe asthma exacerbation provided that there are no contraindications present.^{38,39} The clinician should optimize medical treatment and aggressively treat the patient with beta agonists, corticosteroids and magnesium sulfate. Intubation and conventional mechanical ventilation in the status asthmaticus patient are sometimes necessary. If a trial of NIPPV is to be attempted, it should be done early and the patient should be monitored closely. If there are signs of worsening fatigue or respiratory failure, support should be escalated. Intubation should strongly be considered if the patient fails the NIPPV trial.^{38,39}

Pneumonia

The use of NIPPV in pneumonia is controversial, but in a carefully selected patient, a trial of NIPPV may be attempted. Even with optimal antibiotic therapy and aggressive medical management the course of pneumonia is usually not rapidly correctable. Therefore, standard mechanical ventilation may be a better option than NIPPV. Multiple studies have looked at acute respiratory failure and pneumonia either directly or via subgroup analysis, often with differing results.

One of the larger studies looking specifically at pneumonia patients, conducted by Confalonieri and Potena et al.,⁴⁰ compared 56 patients with acute respiratory failure secondary to severe community-acquired pneumonia (CAP) with NIPPV versus conventional therapy. They found a decreased need for endotracheal intubation (21% v 50%; $p = 0.03$), and duration of ICU stay (1.8 ± 0.7 days v 6 ± 1.8 days, $p = 0.04$). However, there was no decrease in ICU mortality or 60-day mortality. Furthermore, the applicability of this benefit may be limited to patients with COPD. A *post hoc* analysis suggested that the subset of CAP patients with underlying COPD benefited the most from a trial of NIPPV. In this study, patients with COPD treated with NIPPV versus conventional therapy had a decreased need for intubation (0% v 55.5%), duration of ICU LOS (0.25 ± 2.1 days v 7.6 ± 2.2 days, $p = 0.02$), and 60 day mortality (11.1% v 62.5%, $p = 0.05$). A reduction in intubation, duration of ICU stay, and mortality was *not* seen in patients without COPD.

In an observational study looking at NIPPV in 24 patients with severe community acquired pneumonia, Jolliet et al.,⁴¹

found that NIPPV was associated with a moderate improvement of $\text{PaO}_2/\text{FIO}_2$ ratio and a decrease in respiratory rate. A large proportion (66%) of patients eventually required intubation and 8 of those patients expired. Likewise, those patients that did not require intubation had a shorter ICU stay (6 v 16 days) and hospital stay (9.5 v 23 days).

Studies looking at all-comers with hypoxic respiratory failure have found conflicting results with regards to the use of NIPPV in patients with pneumonia. In a study of 64 patients with acute respiratory failure from multiple different causes by Honrubia et al.,⁴² a small subset of 8 patients with pneumonia all failed a NIPPV trial and required mechanical ventilation. In the Antonelli and Conti et al.⁴³ study of 354 patients with acute hypoxemic respiratory failure, the presence of CAP was an independent predictor of NIPPV failure, with 50% requiring intubation. Ferrer et al.,⁴⁴ looking at the use of NIPPV versus conventional therapy in 105 patients with acute hypoxemic respiratory failure, showed a decreased need for intubation (26% v 73%, $p = 0.017$) and ICU mortality (15.7% v 53%, $p = 0.030$) in a subset of 34 patients with acute hypoxemic respiratory failure from pneumonia.

The evidence surrounding the use of NIPPV in acute hypoxemic respiratory failure secondary to pneumonia does not provide a clear signal to the clinician. Although patients who avoid intubation do better, this effect may not be related to the efficacy of NIPPV but may rather suggest the obvious, that sicker patients do worse. To complicate matters, with the exception of the sickest pneumonia patients, it may be difficult to initially differentiate the subset of pneumonia patients who may benefit from a trial of NIPPV versus those that should be immediately intubated. In their 2007 guidelines for the management of CAP, the American Thoracic Society (ATS) and Infectious Disease Society of America (IDSA) recommend a “cautious trial” of NIPPV in patients with CAP that have signs of respiratory distress and/or hypoxemia unless they are candidates for immediate intubation as evidenced by severe disease, bilateral infiltrates, or a $\text{PaO}_2/\text{FIO}_2$ ratio ≤ 150 .⁴⁵ The ATS/IDSA guidelines note that severe CAP and acute respiratory distress syndrome (ARDS) may be hard to distinguish clinically early in the disease process, and NIPPV has poor efficacy in ARDS (see below), further decreasing the benefit of NIPPV in these patients.⁴⁶

A short trial (1 or 2 hours) looking objectively for signs of improvement or failure of NIPPV (fatigue, accessory muscle use, change in PaO_2 , and PaCO_2) may be warranted in the appropriately selected patient with pneumonia. Similar to COPD and CHF, NIPPV may be most useful in pneumonia patients *earlier* in the disease course.⁸ The clinician should anticipate that there is a possibility that the patient with CAP will fail their NIPPV trial and should take the appropriate steps to be prepared to endotracheally intubate the patient in the event of decompensation or failure to improve. However, if intubation can be avoided, there is a higher likelihood of favorable outcomes and decreased associated morbidity and healthcare costs. Again, patients with evidence of severe disease or any evidence of hemodynamic instability, septic

shock, or additional non-pulmonary organ failure, should *not* be considered for NIPPV.¹¹

ARDS

The use of NIPPV in ARDS draws many parallels to the previously discussed use of NIPPV in pneumonia. Similar to pneumonia, the evidence for the benefit of NIPPV in ARDS is not straightforward. Studies looking at the use of NIPPV in ARDS have shown rates of intubation or failure of NIPPV ranging from 46% to 85%.^{42–45} NIPPV may not be as efficacious at preventing intubation in ARDS when compared to COPD, CHF and other disease processes. With regard to the following research studies, all included patients were relatively stable and not in shock. In addition, the sickest patients were endotracheally intubated immediately, before they had a chance of enrolling in the respective studies. Looking at patients with ARDS in multiple studies, NIPPV could be applied to only about 30% of patients with ARDS, and only succeeded in half, or about 16% of total ARDS patients. Therefore it should be clear that the use of NIPPV in ARDS applies to only a very specific, and small, subset of the ARDS population.

Looking at 354 patients with acute hypoxemic respiratory failure, and in particular 86 patients with ARDS, Antonelli⁴³ found the presence of ARDS, and P/F ratio ≤ 146 to be predictors of NIPPV failure. Patients with pulmonary and non-pulmonary causes of ARDS required intubation about 46% and 54% of the time respectively. Stated differently, NIPPV was successful in preventing intubation in ARDS patients approximately half of the time. Half of the ARDS patients who avoided intubation survived, versus 9.5% of ARDS patients who were intubated. It is difficult to make conclusions about mortality benefit from this study because of its uncontrolled nature. Rather the mortality difference may simply prove that sicker patients do worse.

In the Ferrer study⁴⁴ of 105 patients with acute hypoxemic respiratory failure, 15 patients met the criteria for ARDS. Nearly all of the patients who required intubation, in both the NIPPV and supplemental oxygen group, expired. The results from both groups were equally dismal from a clinical standpoint and not statistically different. It is difficult to draw useful conclusions from such a small group of patients, however, these results suggest that NIPPV is less helpful in the treatment of ARDS than other disease states.

Rana et al. in 2006⁴⁶ conducted an observational cohort study examining the use of NIPPV in patients with acute ling injury (mild ARDS based on the 2012 Berlin criteria).⁴⁷ In analysis of 54 patients, 70.3% failed therapy with NIPPV and required intubation and standard mechanical ventilation. All 19 patients in shock failed the NIPPV trial. Additionally, patients with severe hypoxemia as evidenced by a median $\text{PaO}_2/\text{FIO}_2$ ratio < 112 (70–157), and metabolic acidosis (base excess - 4.0, range - 7 - 0.2) had a higher incidence of NIPPV failure. While there was no control group in this study, it seems prudent to bypass a NIPPV trial and proceed directly to ETI and standard mechanical ventilation in patients with evidence of shock and metabolic acidosis.⁴⁸

Antonelli and Conti et al.⁴⁹ in 2007 looked at the use of NIPPV as first line therapy in 147 patients with ARDS who were not intubated. NIPPV was successful in avoiding intubation in 79 patients (54%). Multivariate analysis showed that a Simplified Acute Physiology Score (SAPS II) > 34 (OR 3.6, 95% CI 1.66–7.7) and a $\text{PaO}_2/\text{FIO}_2$ ratio ≤ 175 (OR 2.34, 95% CI 1.1–5.15) after 1 hr of NIPPV were independently associated with NIPPV failure and the need for ETI. The ICU mortality rate was 28%, but ICU mortality was significantly higher in those who required ETI, 5% versus 36%, (OR, 21; 95% CI, 6.4 –76.5, $p < .001$). Patients requiring intubation developed severe sepsis or septic shock and VAP more often. Mortality was higher in those that failed the trial of NIPPV and required intubation (54% v 19%, $p < .01$). The authors recommend that patients with less severe disease (SAPS II < 34) and with a $\text{PaO}_2/\text{FIO}_2$ ratio > 175 after 1 hour of NIPPV will likely benefit from continuation of NIPPV, but those that fail to show substantial improvement in oxygenation after a 1 hour trial of NIPPV should be closely monitored with a low threshold for ETI.

In conclusion, there are two important factors that the clinician must consider before placing a patient with ARDS on NIPPV. First, patients with severe disease as evidenced by a severe hypoxemia (P/F ratio ≤ 150), additional non-pulmonary organ failure, or hemodynamic instability with the need for vasopressors or significant fluid resuscitation should *not* be considered candidates for NIPPV as they have a very high likelihood of failure and may do worse with a trial of NIPPV.^{11,48} Second, if the patient does not show substantial improvement within 1 to 2 hours of NIPPV, it is important that the clinician not permit the patient to linger on NIPPV, but rather escalate therapy.^{11,48} A cautious trial of NIPPV can be attempted in a certain subset of ARDS patients with less severe disease who do not have any of the aforementioned high risk factors for failure.

Do-Not-Intubate (DNI)

When considering the use of NIPPV in patients with a DNI, it is important for the clinician to have an understanding of the patient's goals of care as well as the underlying disease process responsible for respiratory distress. Some patients and their families may be amenable to an attempt of NIPPV, however some may consider NIPPV to be unnecessary "life support" that merely prolongs suffering. The treating physician should explain the risks and benefits of NIPPV and determine the patient's and family members' wishes. NIPPV may alleviate dyspnea and air hunger *or* may worsen discomfort. As with any other patient placed on a trial of NIPPV, the clinician should frequently reassess the patient for evidence of NIPPV failure or success. In DNI patients, failure of NIPPV trial warrants escalation of opiate and other palliative measures in conjunction with the patient's and family members' wishes. Similar to other patients placed on NIPPV, DNI patients with more reversible disease processes causing respiratory distress (i.e. COPD and CHF exacerbations) have more success with NIPPV than those with disease states such as pneumonia or ARDS.

Levy et al. (50) in 2004 looked at the use of NIPPV in 114 patients with DNI status. 43% of these patients survived to hospital discharge. The presence of a strong cough (OR 0.16, 95% CI 0.05–0.51), being awake (OR 0.18, 95% CI 0.05–0.62), having a high baseline Pco_2 (OR 0.01, 95% CI 0.01–0.93), having COPD (OR 0.31, 95% CI 0.10–0.90) or having CHF (OR 0.14, 95% CI 0.02–0.75) as the underlying cause of respiratory failure had better outcomes in terms of hospital mortality. Patients with CHF and COPD survived to hospital discharge approximately 75% and 50% of the time respectively. Patients with pneumonia, cancer, and other diagnoses did poorly, with less than 30% surviving to hospital discharge.

Schettino et al.⁵¹ in 2005 found similar results in their observational trial of NIPPV in 131 patients with DNI status. Patients treated with NIPPV for COPD exacerbations had a hospital mortality rate of 37.5%, and those treated for an exacerbation of ACPE had a hospital mortality rate of 39%. However, patients had significantly higher mortality rates when treated with NIPPV for other conditions such as: non-COPD hypercapnic respiratory failure (68%), post-extubation respiratory failure (77%), advanced cancer (85%), and hypoxemic respiratory failure (86%). In addition, Schettino et al.⁵¹ found that a baseline albumin ≤ 2.5 g/dL or a SAPS II score > 35 also predicted mortality.

In 2007, the Society of Critical Care Medicine Palliative Noninvasive Positive Pressure Ventilation Task Force⁵² put forth a stratification system for the use of NIPPV in DNI and palliative care patients. They proposed three broad classifications of patients with acute or chronic respiratory failure that NIPPV can be used in: patients without preset limits for life support, patients with a preset limit for life support (i.e. a DNI order), or patients that desire comfort care only. Each separate category should have different goals of care, definitions of success, type of escalation in case of failure, and the appropriate clinical setting where NIPPV may be used.

The first category, patients without preset limits for life support, are the standard group of critical care patients with respiratory failure that have no restrictions on care and therefore require all appropriate life sustaining measures. In this group, the goal of care is to restore health. NIPPV can be used for these patients as a means to assist with ventilation and oxygenation as well as to prevent intubation. If NIPPV fails, patients in this category should be endotracheally intubated. According to the task force, these patients should be cared for in an ICU or step down unit setting.⁵²

The second category, patients that request life support but place a limit on care (DNR/I), are patients with respiratory failure where the use of NIPPV may prove to be most beneficial. The goal in this group of patients is also to restore health if possible, with a secondary goal of minimizing discomfort. If NIPPV fails in this category of patient, palliative measures should be initiated, and NIPPV should be discontinued. These patients should also be cared for in an ICU or step down unit setting, however local institutional practice and resource availability should be taken into consideration.⁵²

The final category involves patients who desire comfort care and palliation of symptoms. The use of NIPPV in this

group is controversial, and there is little data to support the use of NIPPV in this situation.⁵² However, NIPPV may be helpful in improving dyspnea and cognition. In these situations, the use of NIPPV can be discussed with the patient and family members. If NIPPV fails to improve dyspnea, or the patient loses consciousness, NIPPV should be discontinued as other palliative measures are pursued. These patients can be cared for in an ICU or step down setting, but a more appropriate locale is probably a hospice or palliative care unit with properly trained personnel. The delineation of these categories is helpful when discussing treatment options and goals of care with patients and family members in order to ensure that the proposed treatment is congruent with their wishes.

In conclusion, the use of NIPPV can be considered in select patients who have a DNI status. An honest discussion should take place between the clinician and patient or family members to ensure that this level of treatment is acceptable. Patients who have respiratory failure secondary to a COPD or CHF exacerbation are most likely to benefit from NIPPV. As with all patients on NIPPV, they should be closely monitored for signs of NIPPV failure. If NIPPV failure occurs, care should focus on comfort and NIPPV should be discontinued.

Delayed Sequence Intubation

There are multiple complications that can develop during the peri-intubation period and recent practice in emergency airway management has put an emphasis on avoiding peri-intubation hypoxemia.⁶ Different techniques have been developed to try and ameliorate and prevent peri-intubation desaturation: high flow preoxygenation, apneic oxygenation, and delayed sequence intubation (DSI) with CPAP.^{6,53}

Classic rapid sequence induction (RSI) employs a preoxygenation period where the patient breathes oxygen via a non-rebreather face mask. After a sufficient time period of denitrogenation and preoxygenation, an induction agent and paralytic are administered in quick order and the patient undergoes intubation. Time to desaturation depends on patient physiology during apnea and the time to tube placement. Advances to this technique include preoxygenation with high flow nasal oxygen and maintenance of high flow oxygen during the apneic period.

However, an important subset of patients, because of underlying shunt physiology, will not improve oxygen saturation with supplemental oxygen or will not improve oxygen saturation to a sufficient level to allow a safe apneic period for intubation without desaturation.⁶ In these situations, CPAP can be used in the peri-intubation period to improve preoxygenation and help prevent oxygen desaturation.^{6,53}

In patients where supplemental high flow oxygen is not sufficient to improve oxygenation, CPAP can be used to increase mean airway pressure, recruit alveoli, and decrease shunt. This can be done in awake patients prior to induction. In combative or unstable patients a DSI approach can be utilized with a dissociative agent that does not affect respiratory drive (ie ketamine or dexmedetomidine) to facilitate patient compliance with CPAP.⁵³ The CPAP is set at 5 to 10 cm H₂O

to recruit alveoli and improve preoxygenation.⁵³ When an acceptable level of oxygen saturation has been obtained, the patient is paralyzed with a muscle relaxant and intubated. It is important that these patients are closely monitored and that the clinician is prepared to convert from DSI to RSI and intubate at any moment should the clinical condition worsen.

Weingart et al examined the use of DSI in a cohort of 62 ED patients requiring intubation who were unable to be sufficiently preoxygenated because of altered mental status.⁵³ Thirty-nine of these patients required NIPPV with CPAP to obtain acceptable preoxygenation. This technique was associated with an increase in oxygen saturation from 89.9% to 98.8% post DSI. All patients post-DSI increased their oxygen saturation and there were no complications observed in this cohort of patients secondary to DSI.⁵³

SUMMARY

NIPPV has revolutionized the management of ED patients with acute respiratory failure. Patients should be appropriately selected for NIPPV—individuals who are hemodynamically unstable, or are unable to protect their airway are *not* candidates for NIPPV. NIPPV works best in disease processes that are easily reversible. Good clinical evidence supports the use of NIPPV in exacerbations of COPD, ACPE, and acute respiratory failure in the immunocompromised, with weaker evidence for its use in asthma patients. A trial of NIPPV may be attempted in a very select subgroup of patients with hypoxemic respiratory failure secondary to pneumonia or ARDS, but there is a higher rate of failure.

Regardless of the etiology of respiratory distress, NIPPV should be initiated early and aggressive medical management should be used in tandem with NIPPV. Patients on NIPPV should be monitored closely for signs of improvement or failure, and NIPPV therapy should be titrated appropriately to assist the patient with work of breathing, oxygenation, and ventilation. If improvement is not apparent within 1 to 2 hours, or any deterioration occurs, the patient should not be allowed to *linger* on NIPPV. Endotracheal intubation should be performed and the patient should be placed on conventional mechanical ventilation. Patients placed on NIPPV should be admitted to an ICU, a step-down unit, or a pulmonary unit with appropriate monitoring. Disposition will depend on disease etiology and severity, as well as local hospital resources and experience.

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Percutaneous Tracheostomy for the Intensivist

Jonathan L. Marinaro • Keith Azevedo • Bradley D. Freeman

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INTRODUCTION

Percutaneous dilatational tracheostomy (PDT) is one of the most commonly performed ICU procedures. For clinicians performing PDT, knowledge of the pertinent anatomy, indications and contraindications, techniques, potential complications, and postprocedural tracheostomy care are crucial to desirable outcomes. As this book is directed to the EM intensivist, this chapter will focus on PDT for the nonsurgeon.

In 2015, data from numerous studies has clearly shown that PDTs are as safe and potentially superior to surgical tracheostomies (ST) in selected patients. To that end, a December 2014 meta-analysis of ST versus PDT examined studies from 1966 to 2013 to determine if PDT techniques are advantageous over ST. A review of fourteen randomized control trials with 973 critically ill adult patients demonstrated that PDT can be performed faster and reduce stoma inflammation and infection, but PDT is associated with increased technical difficulties when compared to ST.¹

Within the specialty of critical care and the field of medicine as a whole, there is an ever-growing body of literature to support or refute treatment modalities, procedures, and management decisions. In the evaluation of any literature, knowing the limitations, evaluating the methodology, and

understanding the difficulty of performing prospective studies must be taken into account before incorporating the findings of such studies into clinical practice.

ANATOMY AND ANATOMIC ISSUES FOR PATIENT SELECTION

The airway is divided into the upper and lower airways. The upper airway consists of the nasopharynx, oropharynx, and laryngopharynx. The lower airway begins at the vocal cords and consists of the larynx (which includes the cricoid cartilage [the only complete cartilaginous ring in the trachea] and cricoid membrane) and the elements of the tracheobronchial tree. The adult trachea is 12 cm in length and the external diameter of the trachea in the coronal plane is 2.3 cm.² The trachea has a series of 20 “U”-shaped cartilaginous rings; each tracheal ring is 4 mm wide and separated by a 2-mm membranous segment.³ The female trachea is smaller in diameter and length. The general shape of the trachea is ovoid with posterior flattening; yet as one ages, the trachea becomes narrower and deeper (laterally narrower and deeper anterior–posteriorly). In nonobese patients, the trachea is approximately 18 to 32 mm deep from the skin, and the posterior wall of the trachea is 40 to 56 mm deep from skin.⁴

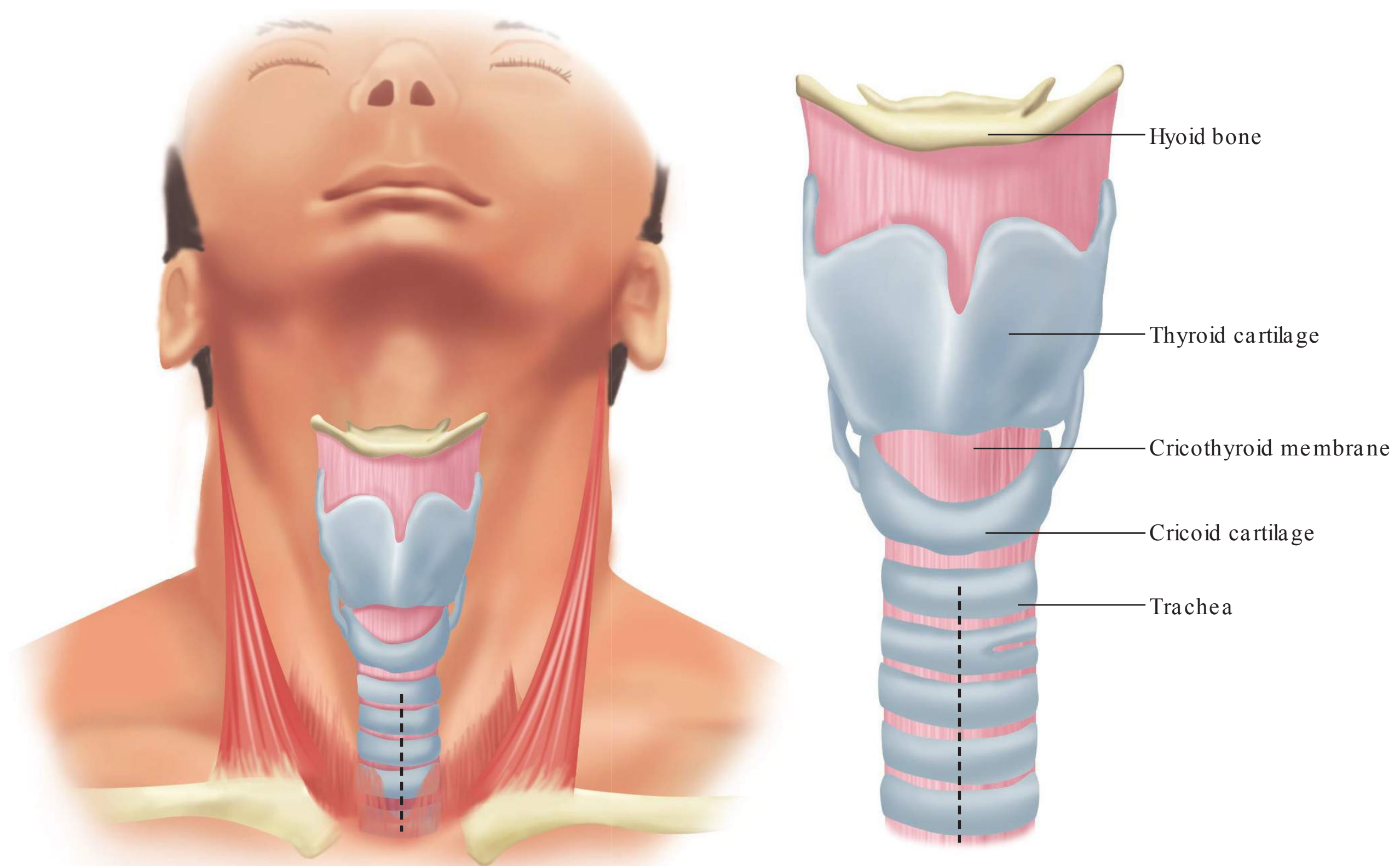


FIGURE 8-1 The skin incision is made in the midline, beginning below the cricoid cartilage and extending down toward the suprasternal notch. An incision made with these landmarks will lie over the second to fourth tracheal rings. (Reproduced with permission from Reichman EF, Simon RR: *Emergency Medicine Procedures*. New York: McGraw-Hill Inc; 2004.)

On bronchoscopic evaluation of the trachea, the cartilaginous rings are seen anteriorly and the longitudinal folds of dense elastic fibers are present posteriorly. Distally, the carina can be seen branching into the right and left main bronchi.

Paramount to performing PDT is the assessment of externally pertinent anatomy (Figures 8-1 and 8-2). Identifying the patient with a short neck, assessing the landmarks in the obese patient, and evaluating potential vascular contraindications

must be completed prior to deciding on PDT. In addition, issues of previous tracheal surgery and cervical spine injury are important anatomic considerations.

The short neck is defined by some as patients with ≤ 3 cm from the sternal notch to the thyroid apophysis (the vocal cords are located posterior to the thyroid apophyseal cartilage).⁵ Other authors have described the short neck as ≤ 3 cm from cricoid cartilage to sternal notch with an extremely short neck as ≤ 1 cm from cricoid cartilage to sternal notch.⁶ A shortened area between the vocal cords and sternal notch may make PDT more difficult to perform and may pose as a relative contraindication to this approach.

Body mass index (BMI) and a resultant thick neck have been evaluated as a possible contraindication for PDT. Byhahn et al. evaluated patients with BMI ≥ 27.5 kg/m² in 73 obese patients and had a 9.6% serious complication rate.⁷ They found obese patients had a 2.7-fold increased risk for perioperative complications, and a 4.9-fold increased risk for serious complications. Contradicting the data of Byhahn et al., Heyrosa et al. performed tracheostomy on 143 patients with BMI > 35 (89 PDT and 53 open tracheostomy) and concluded that PDT in obese patients was as safe as open tracheostomy at their institution. Both open tracheostomy and PDT had 6.5% complication rates.⁸ Mansharamani et al.

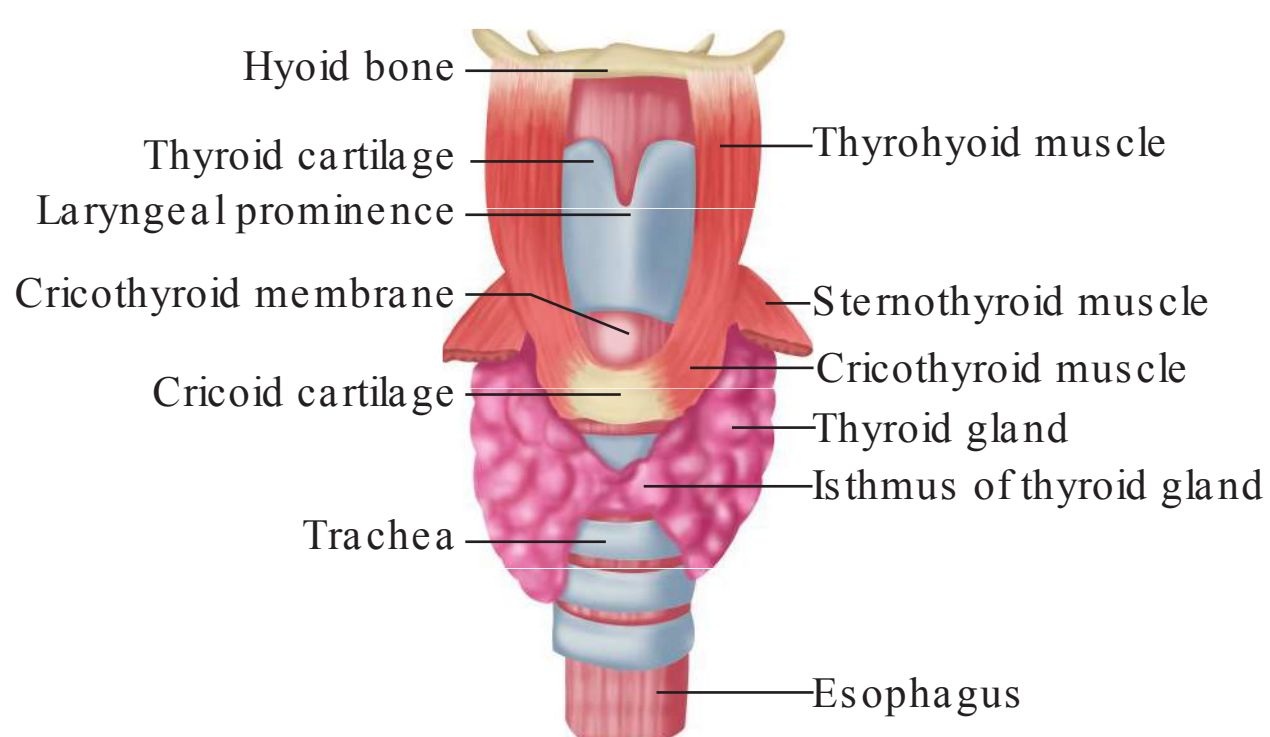


FIGURE 8-2 The framework of the airway in the neck. (Reproduced with permission from Reichman EF, Simon RR: *Emergency Medicine Procedures*. New York: McGraw-Hill Inc; 2004.)

also challenged the BMI data and evaluated PDT in obese patients.⁹

The mean weight was 132 ± 40.8 kg (range 76.8–206 kg), and the mean BMI was 45.9 ± 12.4 kg/m² (range 28.1–61.8 kg/m²). Caution with these data is warranted as only 13 patients were in this series; 3 required an extra long 8-mm internal diameter tracheostomy tube and another required a 9-mm tube. Two patients had complications: cuff leak with need for tracheostomy replacement on day 2 and paratracheal insertion that was readily identified and corrected. More recently, a retrospective review conducted by McCague et al. collected data from 426 patients who were split into two groups (BMI) of < 30 or ≥ 30 kg/m, undergoing PDT to examine blood loss at the time of procedure, difficulty in tracheotomy dilation and/or tracheostomy placement, presence of tracheal ring breaks, bleeding episodes requiring further management via surgery or blood transfusion, pre- and post-procedure pneumonia, and stoma infection requiring antibiotics. Results reported no statistically significant difference in the variables studied among the obese and nonobese group as well as no differences in cohorts using a BMI of 40.

They concluded that PDT may be safely preformed in obese patients.¹⁰ It is important to remember that clinical complications can be challenging to extract from retrospective chart reviews and PDT is an elective procedure that should have equal or less morbidity than the open procedure; therefore, if a patient has poorly identifiable anatomy, it may be wise to consider open tracheostomy.

Because bleeding is the most commonly reported complication in percutaneous tracheostomy, vascular abnormalities overlying the percutaneous route must be evaluated.¹¹ The assessment is based on anatomic understanding of potential vasculature in the area, visual assessment of large pretracheal veins, and ultrasonographic evaluation.

Common sources of bleeding include the thyroid gland, aberrant anterior jugular veins, and unnamed venous vasculature. Visual assessment of large vessels overlying the insertion site should occur, but the addition of ultrasound to this assessment has been proposed and early literature supports ultrasound evaluation prior to incision. In a series of 72 PDTs performed with preprocedural ultrasound, the puncture site was actually changed based on the ultrasound findings in 24% of the patients. None of the cases were complicated by bleeding or posterior tracheal injury.^{12,13} Recent randomized control trials support the early literature findings concerning the utility of ultrasound use in PDT.

The use of ultrasound as an aid for visualizing vasculature in PDT is well known. However, in addition to greater vascular visualization, recent literature reports that primary use of ultrasound for the entire procedure without bronchoscopy shares similar complication rates and clinical outcomes compared with bronchoscopy-only guided PDT.¹⁴ Authors suggest ultrasound may address impaired ventilation resulting from the bronchoscope partially occluding a patient's endotracheal tube, the major obstacle of the arguably standard practiced bronchoscopy-guided PDT using the Ciaglia technique.

Yavuz et al. demonstrated that the use of preprocedural ultrasound guidance before and intraprocedural ultrasound during PDT compared with no ultrasound use can yield an easier and safer procedure with fewer complications; however, it results in a slightly longer procedure time ($n = 341$).¹³ Rudas et al. randomized 50 patients to receive either tracheal puncture procedure using traditional anatomic landmarks or real-time ultrasound guidance, showing significantly improved rates of first-pass puncture and puncture accuracy, further supporting the wider general use of ultrasound guidance as an adjuvant tool to improve PDT.¹⁵

Over the past 15 years, many techniques have been proposed to solve the impaired ventilation problem including: increasing the size of the endotracheal tube (ETT),¹⁶ double lumen ETT,¹⁷ direct laryngoscopy for ETT positioning followed by intermittent bronchoscopy during PDT,¹⁶ PDT without bronchoscopy,¹⁸ and tube exchangers¹⁷ or supraglottic airway devices.¹⁹ However, all of these modifications failed to achieve ideal efficacy over the standard PDT procedure.

In a 2015 editorial in the *Journal of Critical Care*²⁰ Sangwan identified three goals to improve the PDT procedure: provide minimally interrupted ventilation during PDT, minimize accidental extubation and provide optimal visualization of the needle and a dilator upon entering the trachea. It appears that ultrasound-guided PDT could address each of these three goals and two small trials¹⁵ support this idea. But as recent editorials^{14,21} point out, further randomized control trials will be necessary to provide definitive evidence as to the optimal application of real-time ultrasound usage in PDT.

Additional anatomic considerations that must be considered are previous tracheostomy and cervical spine injury. Several small case series conclude that prior tracheostomy is not a contraindication to PDT.^{22–24} The authors perform PDT through prior tracheostomy scars if they are well healed and have not resulted in obvious anatomic distortion. Cervical spine injury is another potential anatomic contraindication to the procedure. In patients with cervical spine fracture, there are two separate risks. Initial risks are in the displacement of the fracture due to the force exerted and positioning for PDT. Mayberry et al. performed PDT on patients with cleared and noncleared cervical spines.²⁵ Thirteen patients had cervical spine fractures, five had halo or operative stabilization, and seven were managed only with a collar prior to the procedure. Neck extension for the procedure was not utilized. There were no spinal cord injuries associated with PDT in this population. The group of seven with nonstabilized neck injuries had a 100% success rate. Ben Nun et al. evaluated 38 patients with cervical spine fracture and, utilizing the modified Griggs procedure, had no PDT-related neurologic deterioration.²⁶ The second risk is in the postoperative patient who undergoes anterior cervical spine surgery.

Without distinction of open tracheostomy versus PDT, Bernie et al. reported that tracheostomy within 4 days of anterior cervical surgery had no increased infection rates.²⁷ O'Keeffe et al., in a smaller study with 6- to 10-day interval between surgical fixation and tracheostomy, found no

cross-infection.²⁸ These small studies suggest the safety of performing tracheostomy in patients with cervical spine fractures and in patients within 7 days of anterior spinal fixation surgery. The authors would like to impress on the reader that, despite these data, the critical care clinician should consider which PDT procedure should be used and have a discussion with the spine service to identify the degree of instability.

TRAUMATIC BRAIN INJURY (TBI)

TBI patients are a subset of critically ill patients who frequently require tracheostomy. These patients have a lower tolerance for hypoxia and hypercarbia, both of which can occur during bronchoscopy and PDT.^{29–31} As hypoxia and hypercarbia may increase intracranial pressure (ICP), thereby decreasing cerebral perfusion pressure (CPP), there are concerns about PDT in TBI patients. Milanchi et al., using paralytics and the Ciaglia method, found no statistically significant change in CPP and ICP during PDT. One quarter of their patients had ICP readings greater than 20 during the 48-hour study period, indicating that at least a portion of patients may have had some cerebral compliance issues that could have been exacerbated.

The study of Milanchi et al. ($n = 52$ had ICP monitoring) agreed with those of Borm and Gleixner ($n = 14$ had ICP monitoring), Escarment et al. ($n = 35$ unclear how many had ICP monitoring), and Imperiale et al. ($n = 65$ had ICP monitoring; “PercuTwist” method) but differed from that of Stocchetti et al. ($n = 30$ with ICP monitoring; 10 PDTs, 10 surgical tracheostomies, and 10 by Fantoni method), who had a statistically significant increase in ICP during all three techniques, yet the greatest frequency in ICP increases occurred in patients with PDT.^{30,32–35}

Conclusions that can be reached from these papers are that tracheostomy and PDT in particular are acceptable in the TBI patient without intracranial hypertension. If a patient has increased ICP and there is a consensus that cerebral compliance is tenuous, waiting until a period of stability would seem a sensible plan. Outside of loss of airway, there is no emergent indication for tracheostomy, and allowing brain pressures to stabilize may incur less cerebral morbidity.

ANTICOAGULATION CONSIDERATIONS

As mentioned previously, bleeding is the most frequent complication of PDT; therefore, evaluation of coagulation studies and withholding anticoagulation would seem to be intrinsic to a successful, low-risk procedure. This too has been challenged. Beiderlinden et al. in 2007 evaluated 415 patients.³⁶ A total of 137 patients had coagulation abnormalities. Fifty-eight patients had a platelet count less than 50,000/mm³, 75 had a PTT > 50 seconds, and 19 patients had a PT > 50% of normal values. Twenty-seven patients had two abnormal values. When the authors divided these patients into acute and chronic bleeding, they found no significant difference in coagulation variables between the acute bleeding

group (defined as occurring during and immediately after the procedure) and the group without any acute bleeding complications.

In evaluating chronic bleeding (defined as persisting for more than 24 hours after tube placement), Beiderlinden et al. found that a PTT greater than 50 seconds predicted a 4-fold increase in chronic bleeding, and platelet count < 50,000/mm³ predicted a 5-fold increase in chronic bleeding. In patients with two or more coagulation variable abnormalities, there was a substantial increase in bleeding (OR = 9.5). In addition, 189 patients had prophylactic low-dose heparin and normal coagulation variables. There was no statistically significant increase in bleeding when compared with the group without heparinization and normal coagulation studies ($P = 0.55$). In the study of Beiderlinden et al., thrombocytopenia was the strongest single risk factor for chronic bleeding. In contrast, Kluge et al. found that platelet counts less than 50,000/mm³ were safe.³⁷ The study by Kluge et al. is confounded by the infusion of platelets just prior to the procedure; therefore, whether these patients truly had low platelets is unknown. In the study by Beiderlinden et al., the thrombocytopenic patients were not treated and as a result definitely had platelets less than 50,000/mm³.

As with many aspects of medicine, the proceduralist's training and past complications will flavor their threshold for proceeding in certain situations. Performing invasive procedures in coagulopathic or heparinized patients is one such situation. Although the study of Beiderlinden et al. is well done and provides interesting data, the question that must be asked is whether missing a single dose of heparin or infusion of plasma or platelets to correct a marginal coagulopathy portends an increased risk of complications such as venous thromboembolism, transfusion reactions, or immunomodulation. Until more prospective data are secured, these decisions will be very practitioner dependent.

VENTILATORY CONSIDERATIONS

The decision to perform tracheostomy is rooted in improving pulmonary function. Since these patients, at best, have some degree of pulmonary dysfunction and may have high levels of ongoing oxygenation and ventilation support, previous recommendations for performing tracheostomy suggested only performing the procedure in the setting of low FiO₂ and low positive end-expiratory pressure (PEEP). PDT inflicts periods of derecruitment and obstruction of the airway. Although in experienced hands these periods are brief, they are not without risk in the unstable patient. Patients who cannot tolerate hypercarbia, hypoxia, or brief loss of airway for cardiovascular reasons are better served by open procedure or delaying the procedure for a period of greater stability.

The benefits of tracheostomy on pulmonary function should be considered. Tracheostomy tubes improve patient comfort and decrease sedative requirements. They can reduce dead space by up to 50% (150 mL) and decrease tube length, reducing work of breathing.

INDICATIONS AND TIMING FOR TRACHEOSTOMY

This section will focus on the benefits of tracheostomy in the avoidance of laryngeal injury from prolonged translaryngeal intubation and shortening the period until liberation from mechanical ventilation.

Prolonged intubation is one of the well-known indications for tracheostomy and is cited as an indication for tracheostomy by the American Academy of Otolaryngology.³⁹ This recommendation is due to laryngeal injury rates as high as 94%⁴⁰ and chronic injury occurring in up to 19% of patients.⁴¹ The long-term sequelae of intubation include stenosis, granulomas, and ulcerations causing chronic hoarseness and, rarely, upper airway obstruction due to stenosis. Tracheal stenosis occurs at the ETT cuff site in one third of the reported postintubation cases. Loss of regional blood flow from high cuff pressures on the tracheal wall creates the ischemic region that leads to scarring. This ischemic injury begins within the first few hours of intubation, and healing of the damaged region by secondary intention can result in densely fibrotic circumferential stenosis over a period of 3 weeks to 6 months. Large-volume, low-pressure cuffs have markedly reduced the occurrence of cuff injury. Tracheal capillary pressure is between 20 and 30 mm Hg, and perfusion impairment occurs at 22 mm Hg and is completely compromised at 37 mm Hg. The recommended cuff pressures are between 10 and 18 mm Hg (15–25 cm H₂O) at all times, and twice-daily evaluation of cuff pressures is advised to limit the occurrence of this devastating sequela.⁴²

Post-tracheostomy tracheal stenosis is also a well-described occurrence. Unlike stenosis secondary to intubation, this can occur due to abnormal wound healing with overgrowth of granulation tissue around the stoma site. It can also occur from granulation at the tip of the tracheostomy tube, or from collapse of the anterior tracheal wall above the tracheostomy stoma. The excess granulation tissue can result from cartilage injury during the procedure or due to unsupported weight of ventilator tubing, creating mechanical strain and ischemia on the cartilaginous ring. Wound infection is an additional cause of post-tracheostomy stenosis.⁴³

The most debated indication for tracheostomy is timing: early versus late, and whether early tracheostomy will shorten ventilator days and ICU stay, and decrease pneumonia rates. In 1989, vague guidelines were published, stating that patients with greater than 21 days anticipated intubation should have tracheostomy and less than 10 days should have translaryngeal intubation.⁴⁴ Between 10 and 21 days, there were no specific recommendations. Since then, multiple studies have attempted to identify whether early tracheostomy may prevent morbidity (see Table 8-1). When evaluating the data, it is important to realize that the definition of early and late tracheostomy can vary widely. Although there are a number of differences between the studies, it seems that duration of mechanical ventilation is statistically shortened with early tracheostomy,⁴⁵ and in one study early tracheostomy had shorter weaning times.⁴⁶ Length of stay (LOS) in

the ICU and/or hospital was also significantly shortened with early tracheostomy in multiple studies. Pneumonia occurrence was reduced by 80% in the study by Rumbak et al. and by 36% in Moller's study.

However, recent literature reports no difference in pneumonia rates.^{46,47,63–65} Additionally, a 2015 Cochrane Review evaluated eight randomized control trials ($N = 1977$ participants) with evidence of moderate quality from seven randomized control trials ($n = 1903$) demonstrating no differences in pneumonia.⁶⁷

Although each of these studies has its limitations due to number of subjects, length of time in the early and late groups, and heterogeneity of population, in certain populations there are expert recommendations for early tracheostomy. Per Eastern Association for the Surgery of Trauma (EAST) guidelines, a Level II recommendation is that patients with severe head injury will benefit from early tracheostomy by shortened ventilator days and ICU LOS.⁴⁸ The guidelines further state that early tracheostomy may decrease the total days of mechanical ventilation and ICU LOS in trauma patients without head injuries and may decrease the rate of pneumonia in trauma patients. Their Level III recommendation is that early tracheostomy be considered in all trauma patients anticipated to require mechanical ventilation for > 7 days.⁴⁸

The guidelines also state, given modern ETTs and protocols keeping balloon pressure < 25 mm Hg, that patients can be safely intubated for at least 14 days.⁴⁸ A more recent review⁶³ evaluating three current randomized trials^{64–66} supported and expanded the 2009 EAST guideline of 14 days. The authors found no benefit in survival, pneumonia, or ICU or hospital LOS for tracheostomy prior to 14 days. The authors conclude that, unless there is a prior clear indication for tracheostomy, clinicians should defer tracheostomy placement for 2 weeks.⁶³

PROCEDURAL CONSIDERATIONS

Bronchoscopy is a useful adjunct in performing PDT for a number of reasons. Most important, any iatrogenic injuries sustained during the procedure can be immediately identified. Inadvertent puncture of the membranous (posterior) portion of the trachea is one such injury that can be avoided. Additionally, a true midline location and directionality for the placement of the wire can be confirmed by direct visualization. Last, appropriate placement of the tracheostomy device itself can be visually confirmed. One pitfall of bronchoscopic guidance is that it requires the ETT tip to be withdrawn to the level of the subglottic larynx. This can create a major cuff leak (since the cuff is no longer past the cords in the trachea) and occasionally loss of airway requiring reintubation. For reasons of patient safety and risk management, most would argue that bronchoscopic guidance and having intubation supplies nearby have become the standard of care.

TECHNIQUES FOR PDT

The basis for almost all percutaneous procedures performed is the modified Seldinger technique, which was originally



TABLE 8-1: Summary of Early Versus Late Tracheostomy Trials

	Type of Study	Sample Size, Early/Late	Timing (Days), Early/Late	Duration of MV (Days), Early/Late	ICU LOS (Days)	Hospital LOS (Days)	Pneumonia Morbidity (%)	Mortality ICU, Early/Late (%)	Mortality Hospital, Early/Late (%)
n	Retrospective	230/231	< 6/> 6	4.7/14.7 (median)	6.8/12.7 (median)	ND	ND	7/14.7	22.2/32.5
	Prospective, randomized	29/31	< 8/> 28	21.5/21.2 (NS)	25.0/24.7 (NS)	ND	96.5/90.3 (NS)	6.9/16.1 (NS)	ND
r	Retrospective	81/104	< 7/> 7	12.2 ± 0.9/21.9 ± 1.3	16.7 ± 1.0/26.0 ± 1.3	23.8 ± 1.2/33.4 ± 1.7	27.2/42.3	ND	ND
ak	Prospective, randomized	60/60	< 2/14–16	7.6 ± 2.0/17.4 ± 5.3	4.8 ± 1.4/16.2 ± 3.8	ND	5.0/25.0	ND	31.7/61.7
	Retrospective	163	< 21/> 21	19.0/44.3	10.8/14.2	ND	43.6/60.4 (NS)	14.5/28.3	44.5/54.7 (NS)
	Prospective database	29/107	< 7/> 7	9.6 ± 1.2/18.7 ± 1.3	10.9 ± 1.2/21 ± 1.3	101 ± 19/105 ± 7 (NS)	ND	3/1 NS	17/14 (NS)
	Prospective, randomized	127/28	3–5/10–14	ND	20 ± 2/24 ± 2 (NS)	ND	49/57 (NS)	ND	24/18 (NS)
erka	Randomized controlled trial	ND	ND	14.5 (SD = 7.3) vs. 17.5 (10.6)	ND	ND	ND	ND	ND
guez	Randomized controlled trial	ND	≤ 7 vs. ≥ 8	12 (SD = 1) vs. 32 (3)	16 (1) vs. 37 (4)	ND	78 vs. 96	ND	ND

intensive care unit; LOS, length of stay; MV, mechanical ventilation; ND, no data; SD, standard deviation; NS, nonsignificant. Adapted with permission from Groves DS, Durbin CG Jr. Tracheostomy in the critically ill: indications, timing and techniques, *Curr Opin Crit Care*. 2007 Feb;13(1):90–97.



utilized for percutaneous nephrostomy tube placement. As a general principle, a needle is used to gain access to a lumen, and through this needle a guidewire is placed into the lumen. The technique for PDT is no different.

Ciaglia Sequential Dilators

The first step is assessment of anatomic landmarks.⁴⁹ The sternal notch, cricoid, and thyroid cartilage are the key landmarks to be identified. Once the skin has been prepped with chlorhexidine solution and the neck draped with sterile towels, the appropriately sized tracheostomy appliance is inspected and the balloon's integrity tested. Beginning at the cricoid cartilage, after infiltration of local anesthetic, a 1- to 2-cm vertical or horizontal incision is carried caudally using a #15 scalpel. Blunt dissection using a hemostat is performed through the strap muscles until the pretracheal space is entered. This is the authors' technique, but many intensivists do not use blunt dissection and perform PDT as purely percutaneous. At this time, the fiberoptic bronchoscope should be inserted. Under direct visualization, after deflation of the ETT cuff, the tube should be withdrawn so that the light from the bronchoscope is visible in the incision site at the level of the second and third or first and second tracheal rings. It is important to remember that in patients who are difficult to oxygenate, this maneuver will likely result in desaturation, and ventilator adjustments will need to be made accordingly.

Utilizing a saline-filled syringe with an 18-gauge catheter over needle, the trachea is pierced below the cricoid cartilage through the incision. Under direct bronchoscopic guidance, the needle should be visualized passing between either the second and third or first and second tracheal rings. Aspiration of the syringe will confirm intratracheal placement by the presence of air bubbles. Bronchoscopy will ensure that the needle does not pierce the posterior wall of the trachea and is anterior midline in position.

Removing the syringe and 18-gauge needle, the catheter is advanced caudally; the flexible guidewire provided in the kit is then visualized by the bronchoscope and passed. The catheter is removed, and the dilators are passed over the wire into the trachea, under direct visualization, from smallest to largest. The largest dilator used is just smaller than the inner diameter of the tracheostomy appliance, instead of a cannula, and is actually placed inside the tracheostomy tube's lumen. Once the tracheostomy tube is completely inserted, the dilator and guidewire are removed, the cuff is inflated, the tracheostomy is connected to the ventilator circuit, and the appliance is sutured into place and secured with tracheostomy ties. At this point, when the new airway has been confirmed, the endotracheal tube is removed completely as well as the bronchoscope.

Blue Rhino™

The Blue Rhino™ or Ciaglia one-step technique, for PDT has rapidly become the most commonly utilized technique

for PDT in the United States. All steps are identical to the sequential dilator technique up to and including placement of the flexible guidewire. The outside of the Blue Rhino™ dilator is hydrophilic and becomes very slippery when wet. Over the wire, a 14 French introducer sheath is placed, and over the sheath/wire combination, the Blue Rhino™ dilator is placed. This dilator has positioning marks, and is curvilinear. Curvilinear pressure is applied toward the mediastinum, creating an appropriately sized tracheostomy opening in a single pass. After this, a curvilinear dilator is placed within the tracheostomy tube; it is placed over the catheter/wire complex, and then the dilator is removed with the wire. As with the previous technique, we recommend bronchoscopic guidance. After this, the tracheostomy tube is secured in a standard fashion. Cook Medical provides an outstanding video of their Blue Rhino PDT at their Web site (http://www.cookmedical.com/cc/educationResource.do?id=Educational_Video).

Griggs

The Griggs technique was developed as an alternative to the sequential dilator technique in 1990.⁵ The technique does not differ until after the insertion of the guidewire, at which point the operator utilizes a sharp-tipped tracheal spreader, which has been designed to slip over the guidewire. These tracheal spreaders are used to create both the soft-tissue tract through the skin and the tracheal opening through which the tracheostomy tube will pass. Following this, a tracheostomy tube with an introducing sheath is passed over the wire, the wire and sheath are removed, and the device is secured into place.

PercuTwist™

Another technique, the PercuTwist™, which utilizes “controlled rotating dilatation,” was described by Frova and Quintel in 2002.⁵¹ A limited number of studies exist that evaluate the efficacy and safety of this technique, although one study, which compared Griggs, Ciaglia, and PercuTwist™ head-to-head, suggests that the PercuTwist™ is not only safe but also significantly faster to perform than the other techniques with a comparable rate of complications.⁵² As with all of the previously mentioned techniques, the trachea is punctured with a needle between the cricoid and first tracheal ring under direct bronchoscopic guidance, and a flexible guidewire is passed through the needle toward the carina. A smaller (8–10 mm) skin incision is made, and the PercuTwist™ hydrophilically coated dilator screw is inserted over the guidewire after being lubricated with water. The clockwise rotation of the screw is stopped after the maximum diameter of the screw has been visualized within the tracheal lumen. After this, the tracheostomy tube, with an introducer sheath through its lumen, is passed over the guidewire, and secured into place. At this point, the wire and introducer sheath are removed.

FANTONI TRANSLARYNGEAL TRACHEOSTOMY

An alternative exists to entering the trachea from the outside. Fantoni and Ripamonti have developed a retrograde percutaneous translaryngeal tracheostomy (TLT), colloquially known as the Fantoni procedure. This is one of the least commonly described techniques in the literature. The trachea is punctured at the usual site; however, the guidewire is passed cephalad and removed through the mouth, and then attached to the dilator/tracheostomy tube complex. This particular dilator has a sharp metal tip; by pulling on the guidewire with one hand and providing countertraction with the other, the metal tip easily punctures the skin, opening the trachea from the inside out. The device is pulled until it is perpendicular to the skin and rotated 180° so that when it is readvanced into the trachea, it will be directed toward the carina. The cannula is removed so that only the tracheostomy tube remains, which is then secured into place. The major advantage of this technique, as described in the literature, is that it has been safely used in children and infants.⁵³ One possible disadvantage of this approach in patients with oropharyngeal malignancy is that stomal metastases have been reported, as the device must pass through the oropharynx and vocal cords.⁵⁴ In a recent comparison of Blue Rhino™ and TLT, complications were not correlated with choice of technique, but the Blue Rhino™ was found to be performed more quickly and in a more cost-effective manner.

COMPLICATIONS OF PDT

Complications of percutaneous tracheostomy must be taken in the context of a comparison to surgical tracheostomy. In a large meta-analysis performed by Delaney et al., PDT was found to have a reduced incidence of infection, and subgroup analysis suggested that there were less periprocedural and long-term complications as compared with open tracheostomy.⁵⁵ Both procedures have complications that the practicing ICU clinician must be aware of; yet the addition of bronchoscopy to the PDT has decreased risks and has become part of the standard of care, as mentioned previously.

During the procedure, there are multiple risks including loss of airway, hemorrhage, injury to tracheal and paratracheal structures, and cardiac arrest. Loss of airway can be a complication that is anticipatable and easily dealt with when proper equipment and personnel who can intubate are readily available. Utilizing the data listed for coagulation studies and understanding potential vascular interference through anatomic knowledge, clinical exam, and ultrasound can limit periprocedural hemorrhage. Tracheal, laryngeal, and paratracheal injuries can best be avoided by understanding the anatomy and utilizing proper technique with bronchoscopic guidance or perhaps real-time ultrasound, with particular focus on midline entry into the trachea, adequate preparation of the skin, and proper technique in applying dilatational pressure in the correct plane. Cardiac arrest that occurs during the procedure may be a result of loss of airway during the pro-

cedure, or the patient being insufficiently stable to undergo the procedure. As mentioned previously, there are no clinical indications for PDT that cannot be delayed if the patient is unstable or an unsuitable candidate for the procedure.

Immediately after the procedure, subcutaneous emphysema (SE), pneumomediastinum (PM), pneumothorax (PTX), tube obstruction, infection, and hemorrhage can occur. SE may be a result of too tight a closure around the tracheostomy tube or prolonged duration of procedure after the point of tracheal perforation and before placement of the tube, or a manifestation of pneumothorax. This highlights why taking a “time-out” to ensure that all important tubes and equipment are in the room prior to incision is important. PTX or PM can occur when there is injury to the pleural domes. This rare complication may lead to tension PTX and therefore supports the need for postprocedure chest radiograph. Tube obstruction can have a number of causes including mucous plugging and abrasion of the inner lining of the trachea, or malpositioning of the tracheostomy tube. The authors have had an instance of PDT in which the friable tissue lining the trachea became a flap that partially obstructed the trachea. That flap caused high peak pressures, and was readily identified and relieved on postprocedural bronchoscopy. The solution to this problem continues to be technique and patient selection.

Infectious complications such as wound infections can be limited by both the PDT technique (as opposed to open surgical tracheostomy) and proper technique including chlorhexidine scrub, and wearing mask, hat, and sterile gloves. Post-PDT cellulitis can be managed with antibiotics and increasing the size of the incision around the tracheostomy tube. Close post procedural evaluation of any surgical intervention should be maintained, and evaluating all tubes, drains, and line sites daily is part of providing good critical care.

Delayed hemorrhage can occur and may be related to vasoconstrictor properties of injected anesthesia that has worn off or, rarely, from the potentially lethal erosion of major thoracic vasculature (0.4% of all tracheostomies), specifically the innominate artery (brachiocephalic artery). Briefly, tracheo-innominate (TI) fistula must be rapidly identified and evaluated if there is any chance to prevent the mortality from this complication.

TI fistula will present most frequently (70% of the time) during the first 3 weeks but can arise as early as 30 hours and as late as several years after the tracheostomy.⁵⁶⁻⁵⁸ Approximately 50% of patients present with a massive hemorrhage, whereas the other half may report a small “herald” bleed⁵⁹ or a pulsating tube.⁵⁸ The most frequent site of fistula formation is at the level of the endotracheal cuff, but one third result from pressure necrosis from the angle or the tip of the cannula. Other predisposing factors include the presence of an anomalous innominate artery, infection, and the use of steroids. Overinflation of the tracheostomy balloon is the first maneuver that should be attempted in the face of a bedside massive hemorrhage. This technique can be successful in 85% of the cases.⁵⁹ Otherwise, a cuffed endotracheal tube should be inserted under direct laryngoscopy into the glottis and beyond the TI fistula.

Finger pressure, directed anteriorly, as the artery is anterior to the trachea, is then applied on the innominate artery through the stomal opening after removal of the tracheostomy tube. For those patients presenting with sentinel bleed, preparation should be made expediently for further evaluation and possible operative repair. A diagnostic flexible bronchoscopy might be attempted first, but a rigid bronchoscopy is recommended for a better visualization and superior ability to suction blood clots. The rigid bronchoscope also allows the operator to stop the bleeding by applying the tube firmly against the innominate artery. The postoperative death rate is relatively high, as only 25% of those who survive the surgery are discharged alive.

Delayed complications that manifest can be less dramatic than loss of airway or TI fistula but must be respected as a serious cause of morbidity and mortality. As mentioned previously, tracheal stenosis, granulation tissue, and laryngeal injury can develop from prolonged intubation or tracheostomy and may or may not be primarily preventable. Although tracheoesophageal fistula is a complication, avoiding trauma to the posterior wall of the trachea during the procedure and abstaining from prolonged large-bore feeding tubes in the esophagus can prevent it. The intensivist can initially manage this rare complication by placing an ETT or new tracheostomy tube distal to the defect yet not too deep to be main-stemmed. Once the airway has been stabilized, a thoracic surgery consult for surgical or nonsurgical management decisions must be undertaken.⁶⁰

A recent case series by Maxwell et al. of 70 patients undergoing PDT via the Blue Rhino™ system serves as an excellent opportunity for synthesis of this section by providing a summarization for minimizing the complications described earlier and thereby maximizing a successful PDT procedure.⁶¹ Maxwell et al. identified four major divisions for minimizing complications and maximizing success: (1) system factors that facilitate training, patient safety, and avoidance of crises; (2) suggestions to prevent loss of the airway; (3) suggestions for avoidance and management of excess bleeding; and (4) strategies to manage common postprocedure problems.

The first divisional recommendation starts with ensuring the appropriate number of personnel are present, which includes two proceduralists: one responsible for the tracheostomy and the other responsible for airway management. The procedure should be conducted during a timeframe in which interdepartmental resources could be utilized if needed (typically during daytime hours at most hospitals). Premedication is part of Maxwell et al.'s first category of patient safety and includes administering chlorhexidine gluconate 1% mouthwash to reduce bacterial colonization and ventilator-acquired pneumonia in addition to giving adequate local and systemic analgesia. The final suggestion for addressing system factors that facilitate training, patient safety, and avoidance of crises is to perform a preprocedural briefing, which should include identification of roles, expectations, and common potential complications.

The second category includes recommendations for preventing loss of airway. These suggestions involve first assessing the airway via chart review to further anticipate possible complications. If a patient is identified as having a difficult

airway, the proceduralist could consider the use of an exchange catheter placed alongside the existing ETT to add an additional margin of airway safety. As with any high-risk procedure, airway equipment should be easily accessible and should include: laryngoscopy equipment (DL and/or video), supraglottic devices such as laryngeal mask airways, styletted ETTs and other airway adjuncts, in addition to instrumentation necessary for performing a surgical tracheostomy. The third category of recommendations centers around suggestions to avoid and manage excess bleeding.

As described in the anticoagulation considerations section of this chapter, no specific consensus guidelines currently exist identifying definitive coagulation thresholds for conducting or cessation of PDT. Therefore, the proceduralist should consider both institutional standards as well as the coagulation concerns outlined previously. Avoiding arterial and venous vascular puncture is clearly integral to mitigating bleeding. Technical considerations include use of ultrasound with color Doppler to delineate vascular anatomy. In addition, some practitioners recommend the use of a vertical midline incision as opposed to a transverse incision.

Finally, the authors recommend having access to a “bleeding kit” which should include the appropriate materials necessary to achieve hemostasis: forceps, silk ties, topical hemostatic agents, and so on. The last set of recommendations includes strategies to manage common postprocedure problems; two of the most common were identified as obstruction and leak of the tracheostomy tube. Malposition may lead to leak or obstruction from the distal portion of the tracheostomy tube being forced against the posterior wall of the trachea or from inadequate depth, necessitating replacement of the tube with a proximal or distal extension device. Although these recommendations are not intended to be a comprehensive or exhaustive list of potential complications and management techniques, they serve as an approach to establishing an organizational framework to promote the safe and effective performance of the procedure.

MANAGEMENT OF THE NEW TRACHEOTOMY TUBE

Accidental decantation (dislodgment) in the first few days after surgery is an emergency. Since the tracheostomy site does not mature until approximately 5 to 7 days post-procedure, these patients should undergo translaryngeal intubation and then be taken to the operating room for reinsertion of the tracheostomy tube. Attempting to replace a new tracheostomy tube into an unmaturing site runs the risk of paratracheal placement, loss of airway, and death. If the patient has a disruption between the upper and lower airways (i.e. post-tumor resection), making mask ventilation and translaryngeal intubation impossible, ventilating through the stoma may be the only choice. This increases the chance of altering the anatomy with subcutaneous air and making the operative replacement significantly more difficult. To prevent accidental tracheal decannulation, the tracheostomy tube should be properly secured, and manipulation and traction

on the tube from oxygen or ventilator tubing should be minimized. Patients should be counseled to move cautiously until the tract is healed.

TRACHEOTOMY TUBE CARE

Knowing how to properly care for a patient with a tracheostomy is vital because inappropriate or inadequate care may lead to complications and even death. Although details vary depending on the type of tracheostomy tube, tracheostomy care includes cleaning or changing the inner cannula, changing the dressing and tracheostomy tube holder, and suctioning if needed. Most tracheostomy tubes have disposable inner cannulas, which are replaced and secured using aseptic technique. Thoroughly assess the skin around the tracheostomy for evidence of skin breakdown related to the tracheostomy tube, tube securement device, or mucus and secretions. The area around the tracheostomy tube should be cleaned with a noncytotoxic cleanser. If you see skin breakdown, consult a wound team for a plan of care. Absorbing secretions helps prevent maceration and skin breakdown.

Place a prepackaged, sterile tracheostomy dressing under the tube flanges. Always use a manufactured, one-layer split sponge rather than cutting a gauze pad. Never place anything with loose fibers around the stoma or tracheostomy tube because they can cause irritation, and the loose fibers could be aspirated.⁶² Maintaining humidification is another key to avoiding potential issues. Normally, the nasopharynx humidifies inhaled air. Because the tracheostomy tube bypasses the upper airway, you need to provide adequate humidity to keep the airway moist. In hospitalized patients, this can be accomplished by a heat and moisture exchanger (HME) on a mechanical ventilator or a T-piece or tracheostomy mask.

Weaning the tracheostomy patient off ventilatory support is the first step for reaching the goal of decannulation. When the patient no longer requires ventilatory support, aerosol tracheostomy collar trials (TCT) should be initiated, and the cuff must be deflated for TCT. During the TCT, there are no ventilator alarms in the circuit to indicate loss of minute ventilation; therefore, it is important to deflate the tracheostomy cuff. If the cuff is inflated, mucous obstruction of the inner cannula will prevent air movement. If the cuff is deflated and inner cannula obstruction occurs, the patient will be able to breathe around the tracheostomy tube and prevent suffocation. The patient should be weaned on oxygen as tolerated.

If the patient has a cuffed tube, the tube should be changed to a cuffless tracheostomy tube. When the patient is able to ventilate and oxygenate adequately with the cuffless tube in place, capping trials should be initiated. If the capping trials are tolerated without any issues for 24 hours, decannulation can be performed. The stoma should be bandaged until closure. The decannulated patient should be followed by the team for 24 hours post-decannulation.

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Extracorporeal Cardiopulmonary Membrane Oxygenation

David A. Farcy • Alan C. Heffner • Lena M. Napolitano

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INTRODUCTION

Despite advances in critical care, severe pulmonary and cardiac failure continue to be associated with high mortality. Out-of-hospital cardiac arrest and acute respiratory distress syndrome (ARDS) continue to have a high mortality rate, as high as 30% to 40%, 50% for patients with cardiogenic shock.¹ Patients failing conventional and advanced and supportive measures have few rescue therapy options. In the late 1960s, prolonged cardiopulmonary bypass support was used to provide extended circulatory support and gas exchange. Out of that work was born extracorporeal cardiopulmonary membrane oxygenation (ECMO), which has been widely used in the neonatal population for conditions such as pulmonary hypertension and meconium aspiration syndrome with a high rate of success. However, in the adult population, this level of success did not hold true until recently.

ECMO is continuing to grow in clinical practice, largely as a consequence of advances in technology. The 2009 H1N1 pandemic and the recent CESAR trial² propagated the use of ECMO worldwide. The new Berlin definition of ARDS provided a separate classification for “severe ARDS” as $\text{PaO}_2/\text{FiO}_2$ ratio < 100 , (refer to the ARDS chapter for more detailed information), which is associated with high mortality rates. ECMO should be considered in these patients (Figure 9-1). This chapter will review the clinical indications for ECMO the different modalities available, the associated complications, and contraindications.

ECMO BACKGROUND AND PRINCIPLES

Cardiopulmonary bypass was developed for use in the operating room to provide short-term support during cardiac surgical procedures. Technological advances in cardiopulmonary bypass to promote longer periods of support started in the 1960s. ECMO and extracorporeal life support (ECLS) refers to cardiopulmonary bypass modified for support over days to weeks.

In most circumstances, ECMO is a rescue technique for patients with imminently lethal disease despite conventional support. Earlier implementation may be used for patients with acute organ failure based on anticipated clinical trajectory. Prime ECMO candidates have acute, severe, but reversible respiratory or cardiac failure. In this context, ECMO provides physiologic maintenance for anticipated native organ recovery. ECMO may also be used to bridge patients with irreversible cardiac or respiratory disease to a more durable form of support such as ventricular assist device (VAD) or heart or lung transplant. Clarification of destination candidacy prior to ECMO initiation is an important step for patients with low probability of native organ recovery.

The ECMO system consists of an extracorporeal circuit, pump, and oxygenator. ECMO configuration and type of cannulation dictates the mode of support, either veno-venous (VV-ECMO) or veno-arterial (VA-ECMO).

Acute Respiratory Distress Syndrome

The Berlin Definition

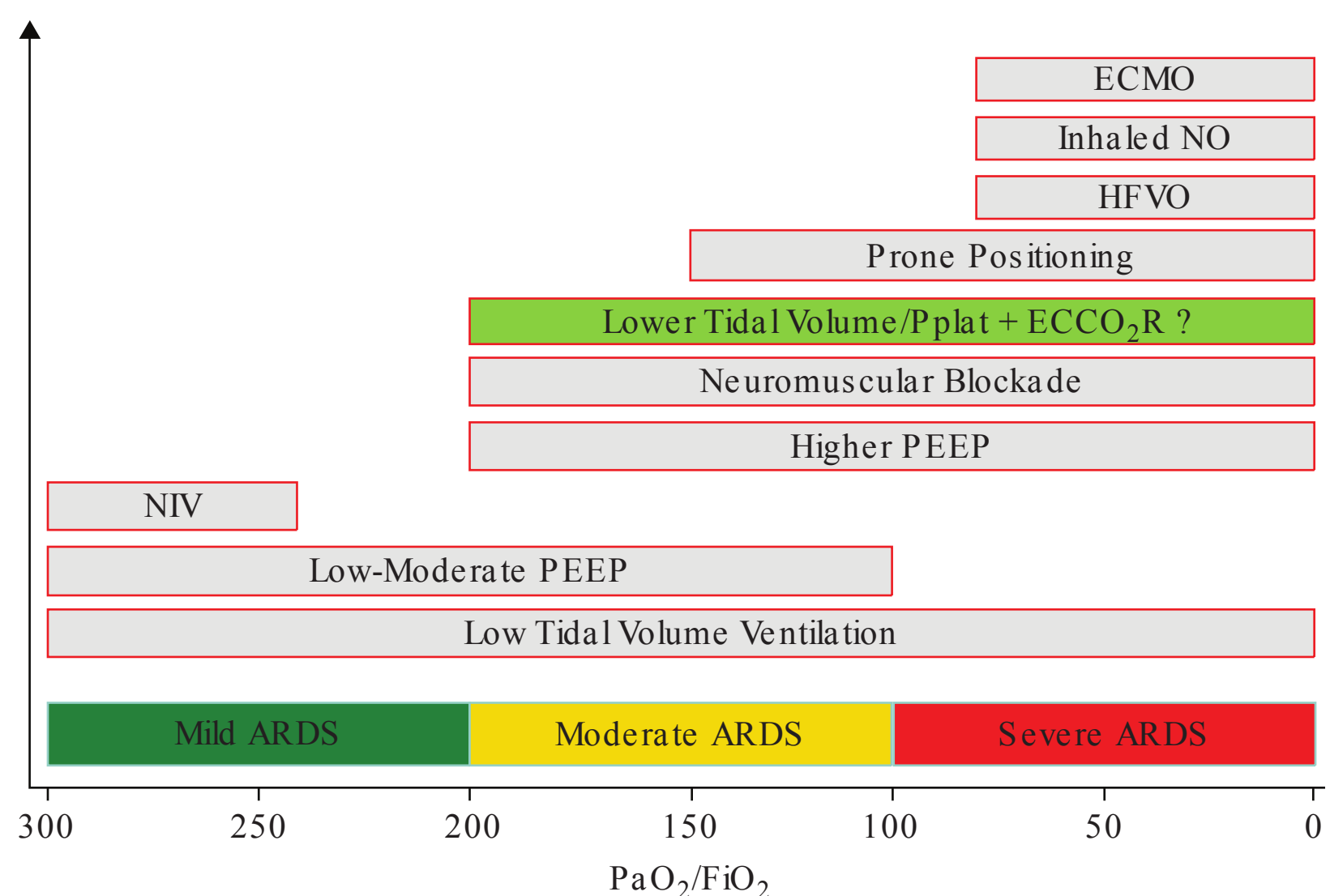


FIGURE 9-1 In the new Berlin definition of ARDS, ECMO is considered as a treatment strategy for severe ARDS, with PaO₂/FiO₂ ratio < 100. (Data from ARDS Definition Task Force, Ranieri VM, Rubenfeld GD, et al: Acute respiratory distress syndrome: the Berlin Definition, *JAMA*. 2012 Jun 20;307(23):2526–2533.)

Venovenous ECMO (VV-ECMO)

Venovenous-ECMO is utilized principally for pulmonary failure and functions by providing membrane oxygenation to temporarily take over the role of the lung for physiological gas exchange by providing oxygen and removing carbon dioxide from the blood. When patients are started on ECMO, the mechanical ventilation settings should be adjusted to decrease the high-transalveolar pressure to minimize ventilator-induced lung injury (VILI) and maximize recruitment of the functional residual capacity. By providing support without reliance on mechanical ventilation for gas exchange, the native lung has time to heal and potentially recover. Additionally, some believe that the injured lung activates the release of inflammatory mediators, which may precipitate renal failure, liver failure, cardiac failure, and other systemic consequences. Release of these inflammatory mediators may be significantly decreased with ECMO support compared with high-pressure mechanical ventilation.³

There is clear evidence of the efficacy of respiratory ECMO for neonates. In 1996, a randomized controlled trial involving 185 neonates with respiratory failure showed a mortality reduction from 59% to 32%.⁴ Subsequently, ECMO has been a common medical therapy in neonatal ICUs around the globe for specific conditions including meconium aspiration syndrome, primary pulmonary hypertension of the newborn, myocarditis, congenital diaphragmatic hernias, and other reversible lung injuries. The use of ECMO in the aforementioned pathologies has yielded survival rates as high as 80%.^{5,6} Similar data have supported the use of ECMO in the pediatric population, with survival rates as high as 73% in pediatric patients suffering from respiratory failure.⁶ The data for cardiac failure in both the neonate and pediatric populations result in a much lower rate of survival than for lung disease, with a quoted rate ranging from 38% to 43%.

However, recently, a very large retrospective review of ECMO for myocarditis in infants, children, and young adults with 255 patients found a 61% survival at discharge.⁸

Unfortunately, the efficacy and safety of ECMO for adults has been less clear and has been debated in the literature. ECMO has been subject to a wide range of opinions in the medical literature since the 1970s, much of which argued that use in adults with ARDS was invasive, expensive, and without any morbidity improvement when compared with mechanical ventilation.⁹ More recent research has begun to change this opinion. In 2004, one large study of 255 adults with severe ARDS who received ECMO revealed a 52% survival rate.¹⁰ A multicenter report from the Extracorporeal Life Support Organization (ELSO, <https://www.elseo.org>) registry included 1473 adult patients who received ECMO for severe respiratory failure. The mean age was 34 years with mean ECMO duration of 144 hours (approximately 6 days). All-cause mortality was reported as 50%.¹¹

The CESAR trial (efficacy and economic assessment of conventional ventilatory support versus extracorporeal membrane oxygenation for severe adult respiratory failure) was a multicenter randomized controlled trial for ARDS patients comparing ECMO versus conventional mechanical ventilation.² A total of 180 patients with ARDS were enrolled. They were randomized to either a tertiary care center or transferred and managed at a single ECMO center. Of the 90 patients who were due to transfer to the ECMO center, only 68 patients actually received ECMO therapy; there was an overall survival at 6 months of 63% for the ECMO group and 47% for the conventional treatment group. This trial has, appropriately, come under scrutiny due to the lack of standardized treatment management in the control group and because the ECMO center observed happened to be one of the most experienced in the world. One can conclude that early transfer to

a specialized ECMO center might increase survivability but well-randomized controlled trials still need to be conducted.

A meta-analysis of the three randomized controlled trials (over a span of 30 years) of ECMO in adult respiratory failure found a summary risk ratio for mortality of 0.93 (95% CI 0.71–1.22) with significant heterogeneity in the trials. The authors concluded that clinicians should consider ECMO within the context of other salvage therapies for severe acute respiratory failure, and that future studies are needed to define the optimal use of this potentially life-saving intervention.¹²

Interestingly, due to the 2009 Influenza A (H1N1) epidemic, there has been a resurgence of reports favoring the use of ECMO in adults, including a large observational report of 68 patients with H1N1-associated ARDS, who received ECMO therapy in Australia and New Zealand.¹³ The ECMO group had severe hypoxemia that was defined by a mean $\text{PaO}_2/\text{FiO}_2$ ratio of less than 60. The ECMO group had originally posted a survival rate of 79% but, in an update of their data, the authors quoted a survival rate of 75% at time of discharge.¹⁴

In another report of patients with H1N1-related ARDS in the United Kingdom, referral and transfer to an ECMO center

was associated with lower hospital mortality compared with matched non-ECMO-referred patients.¹⁵ More recent propensity analyses by the French Réseau Européen de Recherche en Ventilation Artificielle (REVA) research network demonstrated no difference in intensive care unit mortality between patients who received ECMO for H1N1-related ARDS and non-ECMO control subjects (odds ratio 1.48; 95% CI 0.68–3.23, $p = 0.32$), without duplication of control subjects in the matching process.¹⁶ Of note, 51 ECMO patients who could not be matched were younger, had more severe hypoxemia, higher plateau pressures, and lower mortality than the ECMO patients matched to controls (22% vs. 50%, $p < 0.01$). Given all of these results, it is clear that ECMO was an effective treatment strategy for critically ill patients with Influenza A (H1N1) virus infection and severe refractory hypoxemia.^{17,18}

Further research is currently underway. EOLIA, (ECMO to rescue Lung Injury in severe ARDS, <https://clinicaltrials.gov/ct2/show/NCT01470703>) is an ongoing multicenter international randomized controlled trial of ECMO in adults with severe ARDS (Figure 9-2). In the ECMO arm, ECMO is initiated as soon as possible for every patient randomized

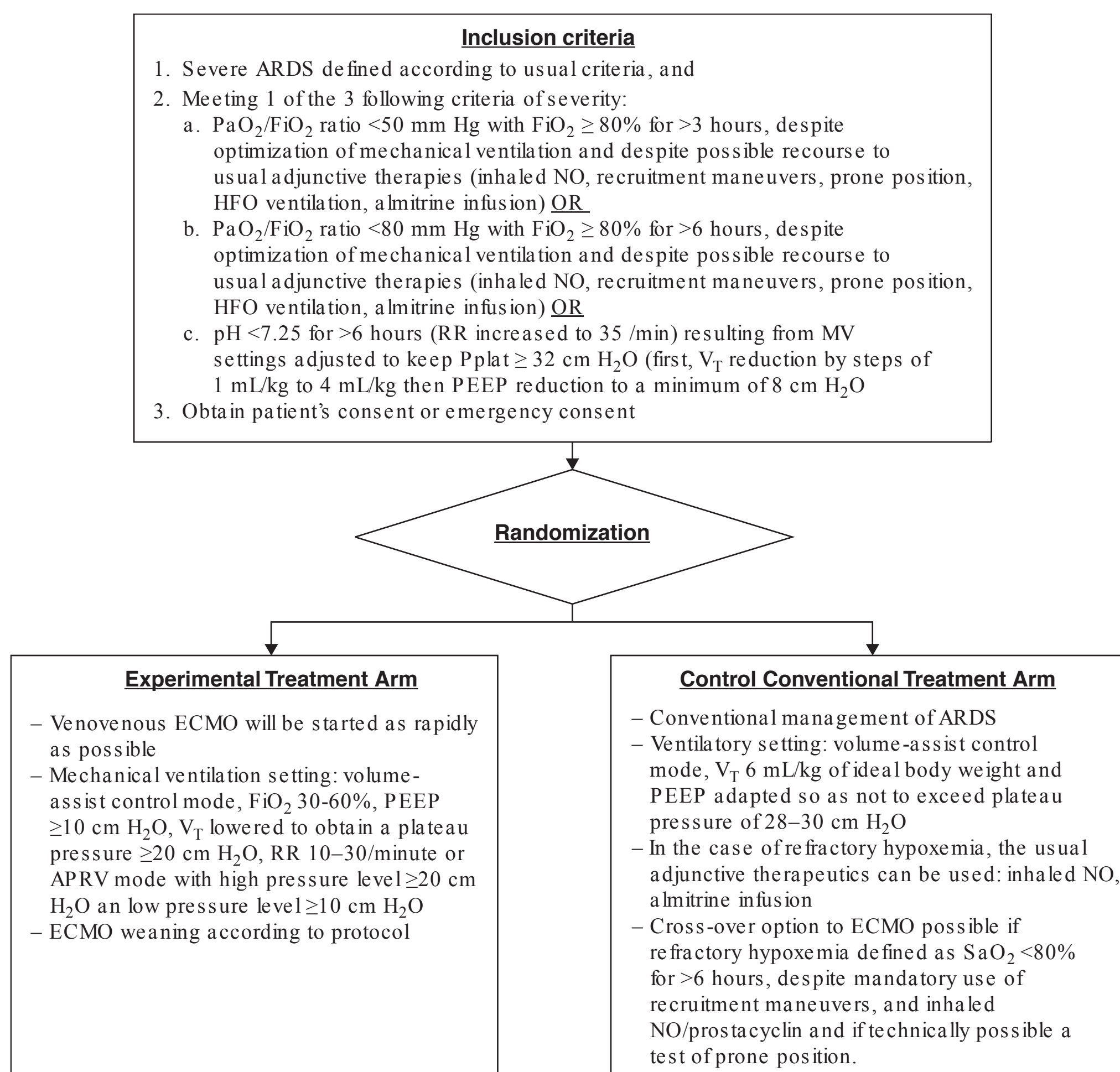


FIGURE 9-2 EOLIA (ECMO to rescue Lung Injury in severe ARDS) multicenter ECMO trial in adult severe ARDS (Alain Combes MD, PI) inclusion criteria and randomization. Primary endpoint: All-cause mortality at day 60. (Reproduced with permission from ClinicalTrials.gov. A service of the U.S. National Institutes of Health.)

using the more recent ECMO technology (CardioHelp-Maquet Cardiovascular LLC, Wayne, NJ, U.S.). ECMO will be managed only in very experienced centers, and highly protective mechanical ventilation is planned with plateau pressure limited to ≤ 24 cm H₂O. The control arm will receive volume-assist control mode with tidal volume 6 mL/kg of ideal body weight and PEEP adapted so as not to exceed plateau pressures of 28 to 30 cm H₂O. Crossover to the ECMO is possible for refractory hypoxemia despite mandatory use of recruitment maneuvers, inhaled nitric oxide and prone position. Currently, the estimated completion date for this study is early 2017.

Venoarterial ECMO (VA-ECMO)

CARDIOGENIC SHOCK

Venoarterial ECMO for refractory cardiogenic shock is considered a successful salvage therapy at present. A single-institution experience of 179 patients documented that 38.6% of patients survived to discharge and 44.7% survived to 30 days. Myocardial recovery was achieved in 79.7% of survivors and 39.1% were transitioned to a more durable device.¹⁹ Similarly, a single-institution retrospective study of 35 patients rescued by ECMO for acute myocardial infarction-induced cardiopulmonary collapse reported an ECMO weaning rate of 63% and a hospital discharge rate of 40%. The major cardiovascular adverse effect-free survival was 77% in the first year after discharge.

This report confirmed that early revascularization on ECMO is practical to preserve myocardial viability and bridge patients to recovery.²⁰ Recent data from an observational analysis confirmed a lack of survival benefit with the concomitant use of intra-aortic balloon pumps with ECMO in patients with cardiogenic shock and cardiac arrest requiring ECMO (37.5% ECMO alone vs. 35.5% ECMO with adjunctive intra-aortic balloon pump).²¹

CARDIAC ARREST

In cardiac arrest, the longer the patient is without any circulation, the worse the outcome. With the recent focus on compression to increase perfusion, but without early initiation of full CPR, mortality has not been affected and remains very high. With the advent of newer, smaller, more portable ECMO machines, the concept of extra-corporeal cardiopulmonary resuscitation (E-CPR) has recently reemerged in the medical resuscitation literature.

Unfortunately, due to the patient population, it is difficult to perform randomized, double-blind trials of ECMO in cardiac arrest. Most of the recently published evidence is from case reports, case series, and observational studies. Shin et al. conducted a retrospective study in Korea of 406 in-hospital cardiac arrest (IHCA) patients, comparing E-CPR with conventional CPR. Patients who had more than 10 minutes of CPR after witnessed in-hospital cardiac arrest were eligible for enrollment based on the team leader's decision. Eighty-five patients underwent E-CPR, compared

to 321 who underwent conventional CPR; the primary end point was survival with a good neurological endpoint. They found that E-CPR was associated with a higher rate of survival without significant neurological impairment upon discharge when compared to conventional CPR: significant neurological deficit hazard ratio was 0.17 (95% confidence interval, 0.04 to 0.68, and p value of 0.012) and survival at 6 months with minimal neurological deficit hazard ratio was 0.48 (95%, confidence interval 0.29 to 0.77; p value = 0.03).²²

Another group, out of Taiwan, performed a similar study on the same patient population, with 122 patients included in their study and 59 in the E-CPR group, and they concluded there was no benefit.²³ Both of these studies evaluated patients with IHCA. IHCA as compared to out-of-hospital cardiac arrest (OHCA) is well known to be of a multifactorial cause, whereas OHCA is primarily from a cardiac arrhythmia in 70% to 85% of affected patients.²⁴

In a case series from San Diego, which initiated E-CPR from the emergency department (ED), 42 cardiac arrests in a one year period with 18 patients met inclusion criteria. Eight were admitted, and five of those patients had neurologically intact survival to hospital discharge.²⁵ Even though this was a small case series, it was the first of its kind in the United States that examined initiating ECMO for OHCA patients.

Further positive evidence was more recently published in the CHEER trial, which was a single-center prospective, observational study to evaluate the safety and efficacy of E-CPR with therapeutic hypothermia. Twenty-six patients were eligible with a mix of IHCA and OHCA, 25 patients had a return of spontaneous circulation (ROSC), and 14 (54%) had survival to hospital discharge with a good neurological outcome, defined by a cerebral perfusion category score of 1. Thus the author concluded that E-CPR is feasible, with a relatively high survival rate.²⁶

For now, there is no clear-cut evidence for the role of E-CPR in cardiac arrest, although its use in experienced centers with the right resources seems to have real promise and needs to be investigated more thoroughly. In general, ECMO may have a role in certain disease processes, but it is not considered the standard of care for adults. Recent studies suggest a mortality benefit when used early if proven ventilation techniques have failed. ECMO is best left to centers that are specialized and that have appropriate resources.²⁶

INDICATIONS

Neonatal

ECMO, as described earlier, is a routine part of neonatal care used in newborn infants for severe respiratory failure commonly associated with primary pulmonary hypertension, meconium aspiration syndrome, congenital diaphragmatic hernia, respiratory distress syndrome, group B streptococcal sepsis, and asphyxia.

Pediatric

Pediatric ECMO is used for respiratory distress syndrome and in low cardiac output situations such as right, left, or biventricular failure following repair of congenital heart defects and with pulmonary vasoreactive crises that can occur following these surgeries. Sometimes ECMO is used as a bridge to cardiac transplant or as a bridge to recovery in temporary cardiomyopathy secondary to renal failure, myocarditis, and burns.

Adult

Common etiologies of adult pulmonary and cardiac failure requiring ECMO support include:

1. Respiratory failure, characterized by severe hypoxemia or impaired ventilation, which includes, but is not limited to:
 - a. Adult respiratory distress syndrome (ARDS)
 - b. Massive pulmonary embolus
 - c. Pneumonia (viral, bacterial, fungal)
 - d. Sepsis
 - e. Multisystem trauma
 - f. Pulmonary contusion
2. Cardiac failure, characterized by circulatory collapse refractory to medical therapy, which includes, but is not limited to:
 - a. Acute cardiomyopathy
 - b. Congenital heart disease
 - c. Right ventricular failure
 - d. Cardiopulmonary arrest
 - e. Biventricular failure
 - f. “Bridge” to transplant

PATIENT SELECTION

Patient selection criteria for ECMO vary from center to center. The usual criteria include patients with a severe but potentially reversible process that would otherwise result in a very high predicted mortality with conventional medical support. See Table 9-1 for indications and Table 9-2 for contraindications.

Unfortunately, patients who are sick enough to require ECMO but do not have access to this therapy often have



TABLE 9-1: Indications for ECMO

- Refractory cardiogenic shock
- Severe hypoxemia or ARDS ($\text{PaO}_2/\text{FiO}_2$ ratio < 100 on FiO_2 1.0)
- Cardiac arrest
 - Inability to wean cardiopulmonary bypass in the operating room
- Bridge to cardiac transplant or ventricular assist device
- Bridge to lung transplant in patients with interstitial lung diseases

Data from Van Meurs K, Lally KP, Peek G, Zwischenberger JB (2005) *ECMO: Extracorporeal Cardiopulmonary Support in Critical Care (The “Red Book”), Third Edition*. Michigan, Extracorporeal Life Support Organization.³



TABLE 9-2: Contraindications to ECMO

The following parameters describe a patient population with a greater than 80% predicted mortality risk from ARDS:

- Mechanical ventilation for ≥ 7 days
- Irreversible cardiac or respiratory failure
 - Active bleeding, or other situation in which anticoagulation is contraindicated
- Poor preexisting functional status
- Irreversible neurologic pathology
- Cardiac patients in whom a ventricular assist device is contraindicated
- Age > 60 years (relative contraindication)

Data from Van Meurs K, Lally KP, Peek G, Zwischenberger JB (2005) *ECMO: Extracorporeal Cardiopulmonary Support in Critical Care (The “Red Book”), Third Edition*. Michigan, Extracorporeal Life Support Organization.³

a mortality rate approaching 100% despite maximizing all other forms of available medical treatment. Early referral to a specialized ECMO center is crucial and should be initiated earlier rather than later into the diseased state. Too often, physicians see this therapy as a “last ditch” effort several days into the diseased state. ECMO is more beneficial when started as early as possible.

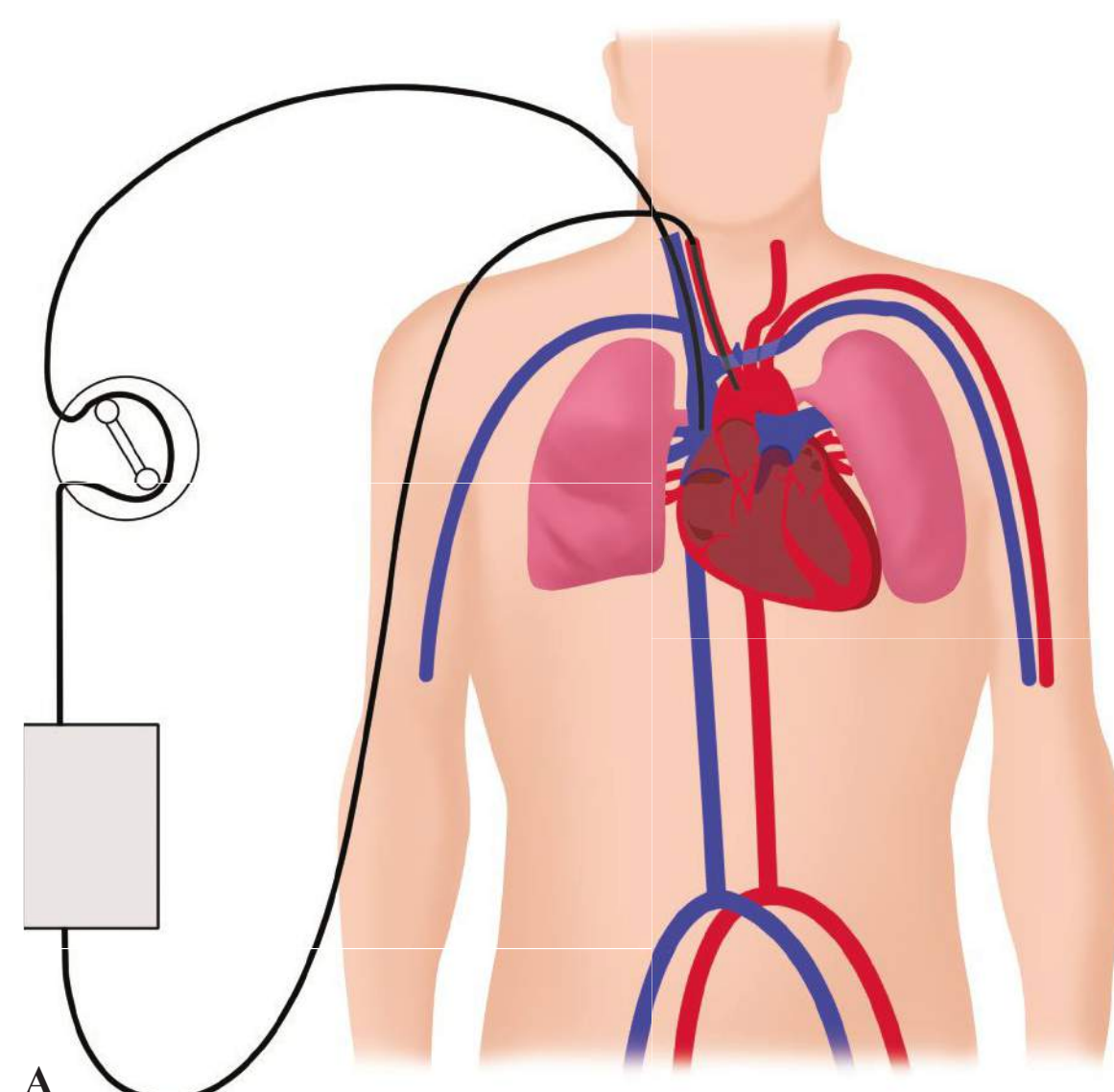
TECHNIQUE AND METHODS

ECMO employs use of a modified heart–lung bypass machine to provide gas exchange and systemic perfusion. The method in which ECMO is used is based on the catheter placements by either VV-ECMO or VA-ECMO (Figure 9-3A–C) bypass. The ECMO catheters, or cannulae, are typically placed by direct cutdown on vessels or by percutaneous introduction of the cannula using sequential dilators and guide wires similar to the technique used in standard central line placement. ELSO guidelines currently recommend a heparin bolus of 50 to 100 units/kg with cannulation and then continuous infusion heparin for systemic anticoagulation.

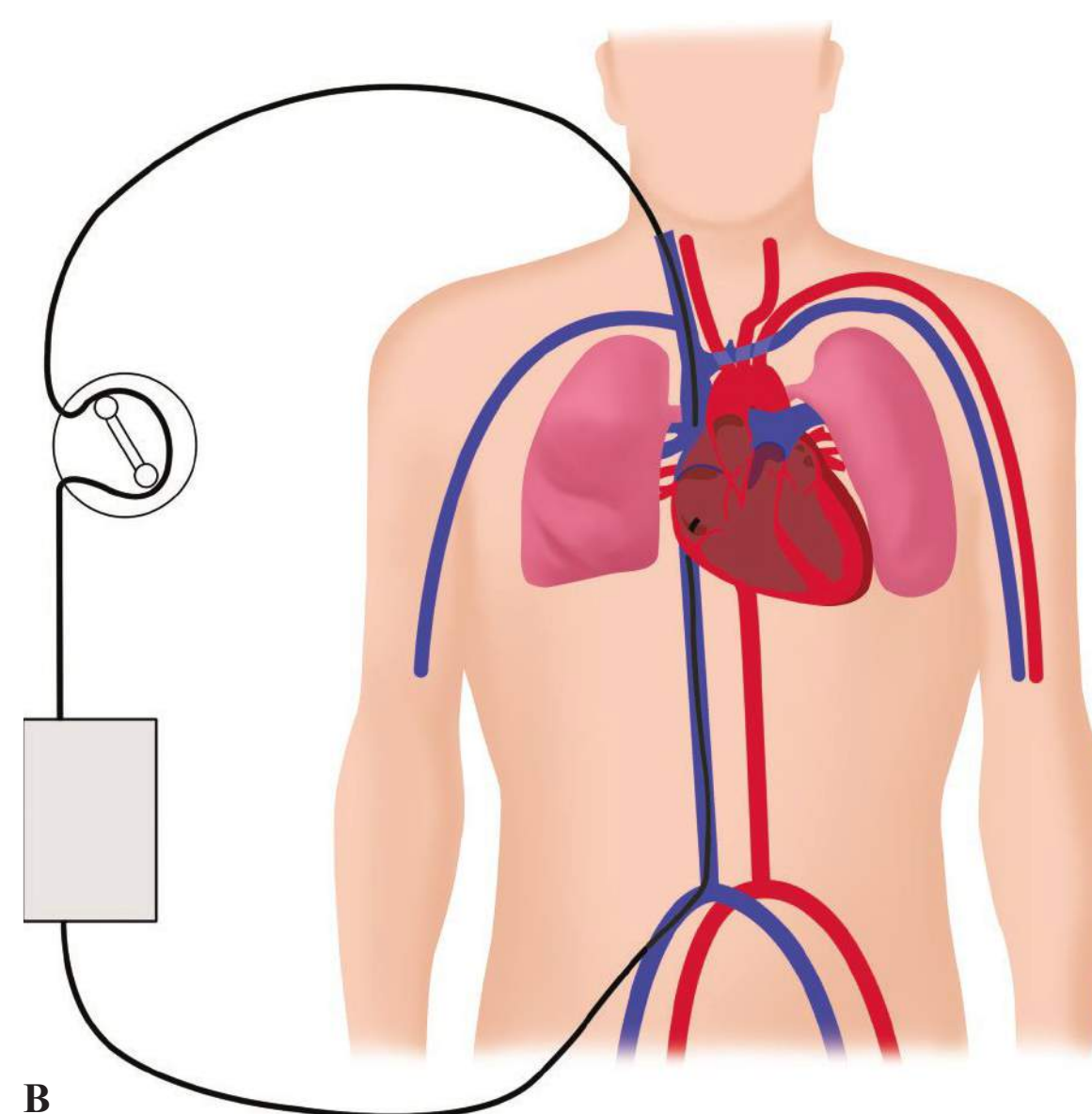
VA-ECMO

In VA-ECMO, the ECMO oxygenator is in parallel with the lung and the “pump” provides both respiratory and cardiac support. Two techniques are currently being used. In the peripheral approach, a catheter (23–30 French) is either inserted peripherally or surgically into the internal jugular or femoral vein to withdraw blood and circulate it through the membrane oxygenator and return the blood through another catheter in the femoral or subclavian artery. If femoral arterial cannulation is used, a distal leg arterial perfusion catheter to restore blood flow to the lower extremity should be considered. An alternative is placement of an ipsilateral posterior tibial artery reperfusion cannula via a small incision behind the medial malleolus in a retrograde manner, connected to the arterial limb of the ECMO circuit within 6 hours of cannulation.²⁷

The central method requires surgical placement of a catheter that withdraws blood directly from the right atrium and

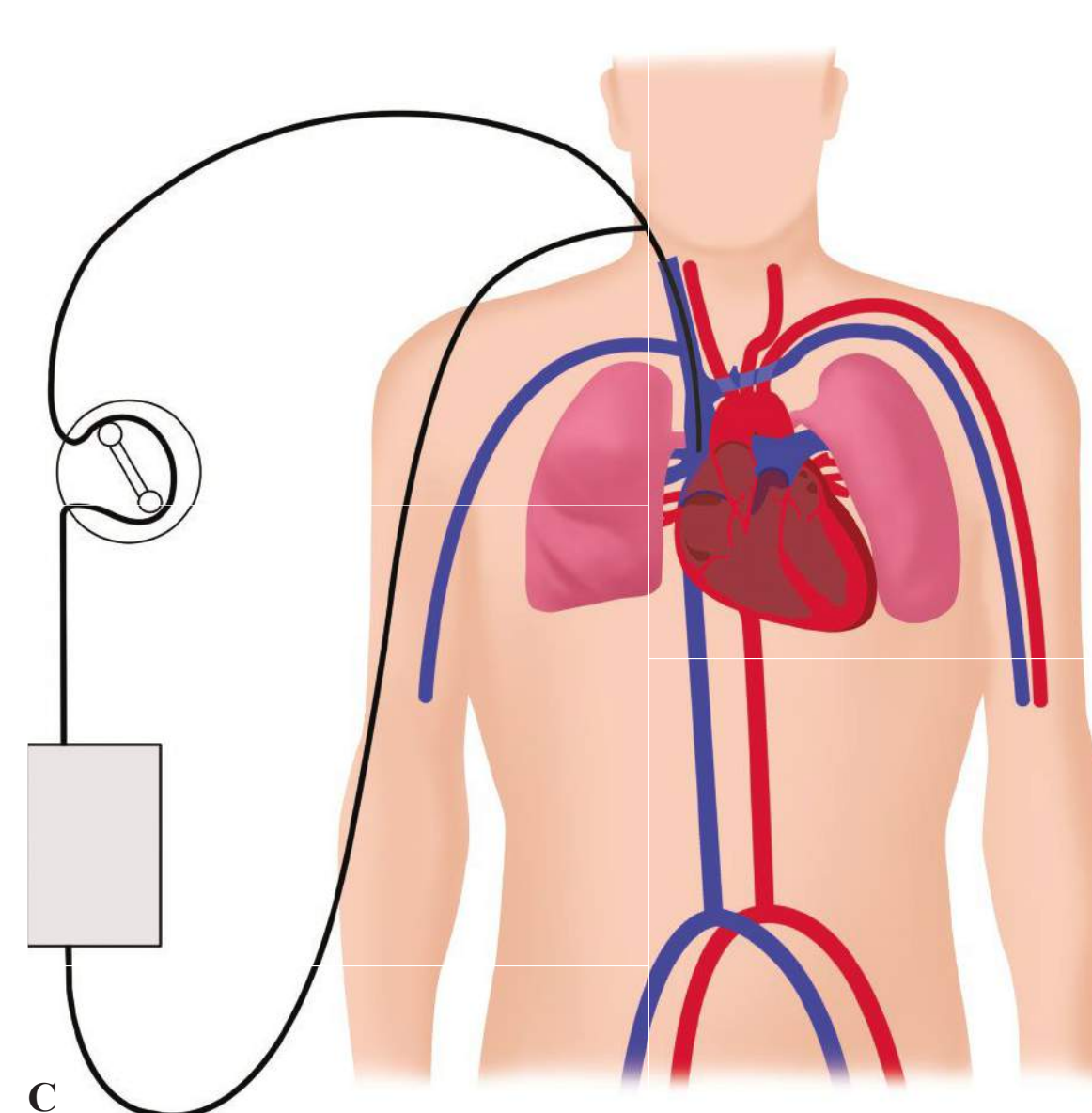


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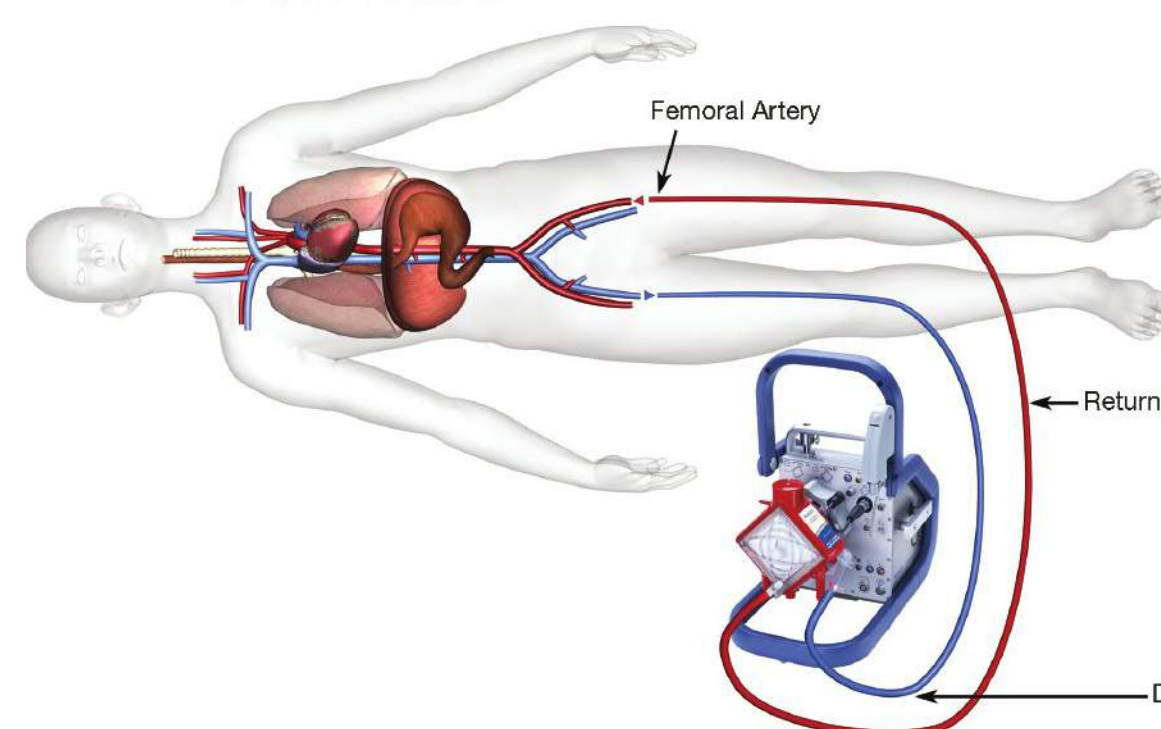
B

FIGURE 9-3 **A.** VA-ECMO. Venous drainage occurs through right internal jugular vein. Arterial return occurs through the common carotid artery into the aortic arch or via the femoral artery. **B.** VV-ECMO can be accomplished via a traditional approach (with two venous cannulae, usually right internal jugular and right femoral veins, which can be performed bedside in the ICU or ED) or **C.** via a single dual-lumen cannula placed via the right internal jugular vein (which generally requires placement via fluoroscopy). ((C) Used with permission from Maquet Cardiopulmonary GmbH) **D.** VA-ECMO and **E.** VV-ECMO on Maquet System. (D-E Used with permission from Maquet Cardiopulmonary GmbH.)



C

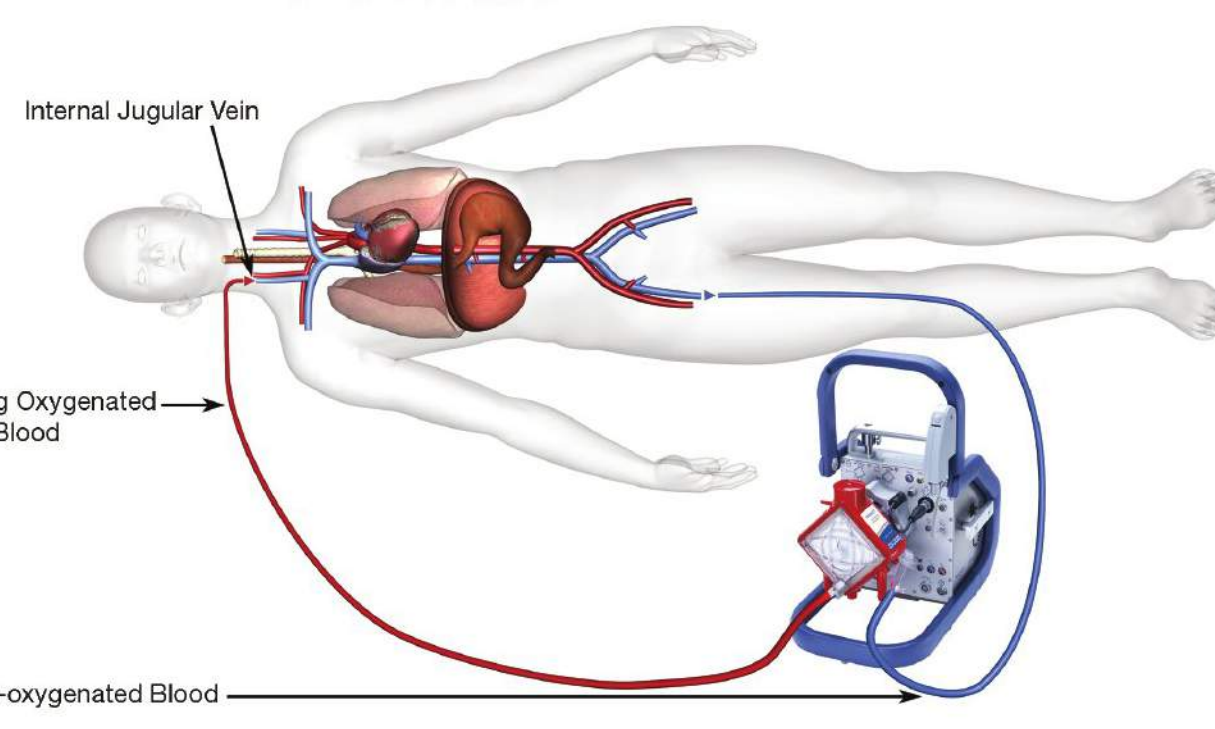
V-A ECMO



D

Venous drainage of deoxygenated blood from the femoral cannula (ideally in perihepatic inferior vena cava); Arterial return of oxygenated blood via femoral artery cannula into right atrium.

V-V ECMO



E

Venous drainage of deoxygenated blood from right femoral cannula (ideally in perihepatic inferior vena cava); venous return of oxygenated blood via right internal jugular cannula into right atrium

© Maquet Cardiopulmonary GmbH

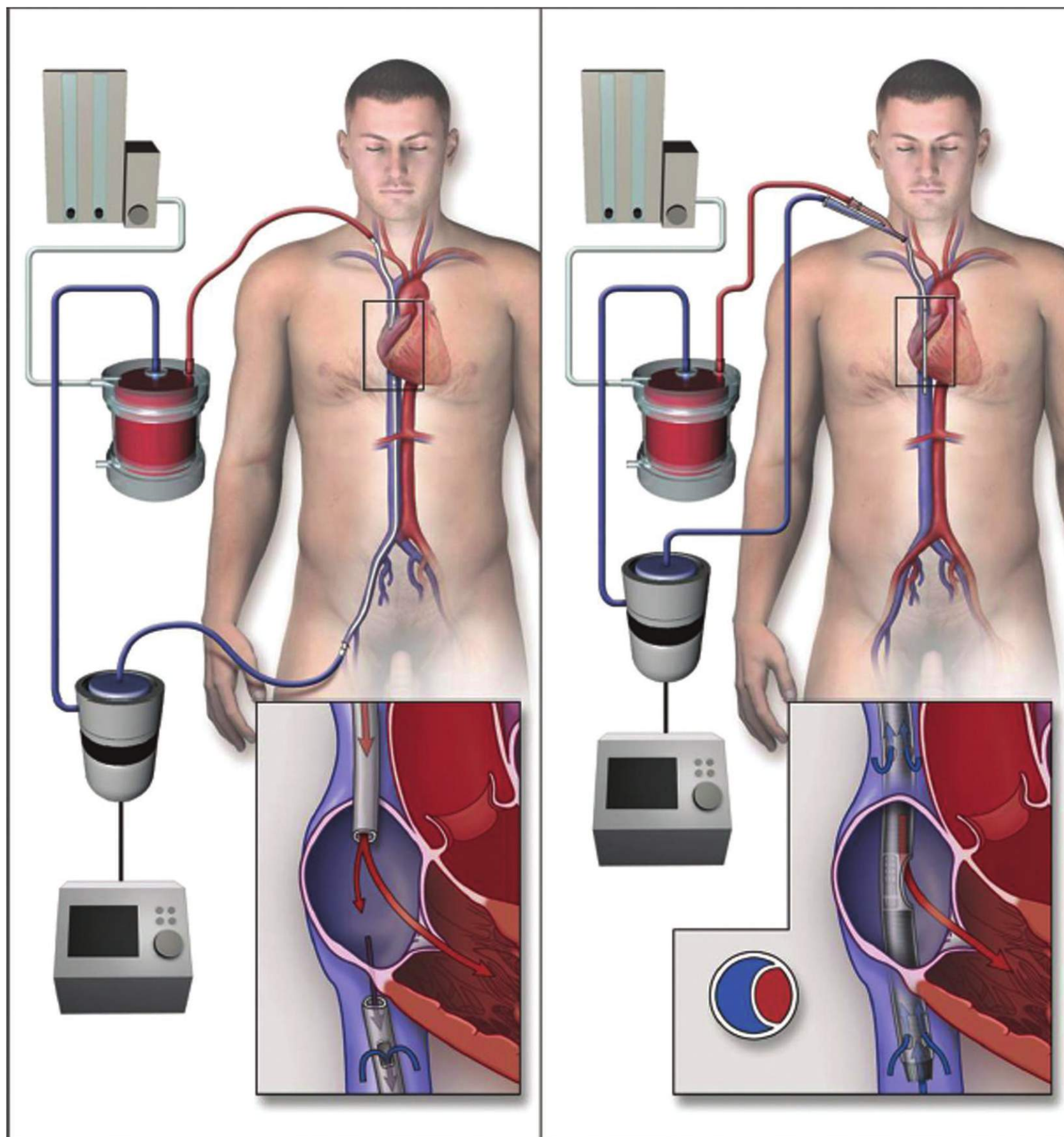


FIGURE 9-4 Traditional VV-ECMO cannulation (separate right internal jugular and femoral veins) vs. dual-lumen cannula (31 French). Advantages to dual-lumen cannulation includes less mixing, no “streaming,” less recirculation and ability for patient to ambulate. Dual-lumen ECMO cannulation requires fluoroscopy for placement. (Reproduced with permission from Brodie D, Bacchetta M: Extracorporeal membrane oxygenation for ARDS in adults, *N Engl J Med*. 2011;365:1905–1914.)

returns the blood through a catheter in the aorta. The VA-ECMO circuit requires high flow, typically 100 mL/kg/min to maintain support. Since blood flow through the patient’s native heart and lungs is diverted to the ECMO circuit, the patient’s cardiac output is controlled by the amount of blood that travels through the circuit. In VA-ECMO, the ECMO flow determines the cardiac output and oxygen delivery. Thus, VA-ECMO can provide pulmonary and cardiac support.

VV-ECMO

In VV-ECMO, the ECMO oxygenator is in series with the native lungs and the circuit provides only respiratory support without any cardiac support. VV-ECMO diverts the patient’s blood from the venous circulation and returns it to the venous circulation. VV-ECMO cannulation can be accomplished via two approaches: two separate venous cannulae with inflow into the right atrium via the right internal jugular vein or the femoral vein and outflow via the femoral vein and inferior vena cava, or a single bicaval dual-lumen ECMO cannula in the right internal jugular vein (Figure 9-4). Significant advantages to the single dual-lumen ECMO cannula for VV-ECMO in adult respiratory failure are decreased recirculation and the ability to achieve early mobility and ambulation.

The Avalon ELITE Bi-Caval Dual Lumen Catheter® (Figures 9-5 and 9-6) is a single large (31 French) multi-perforated drainage cannula, inserted into the internal jugular vein matching the body’s natural flow ratios by



FIGURE 9-5 Dual-lumen ECMO cannulation via a percutaneous right jugular vein approach using a 31 French Avalon ELITE Bi-Caval Dual Lumen Catheter®. Note the color difference in deoxygenated venous outflow and oxygenated venous inflow blood in the two lumens. (Used with permission from Lena Napolitano MD.)

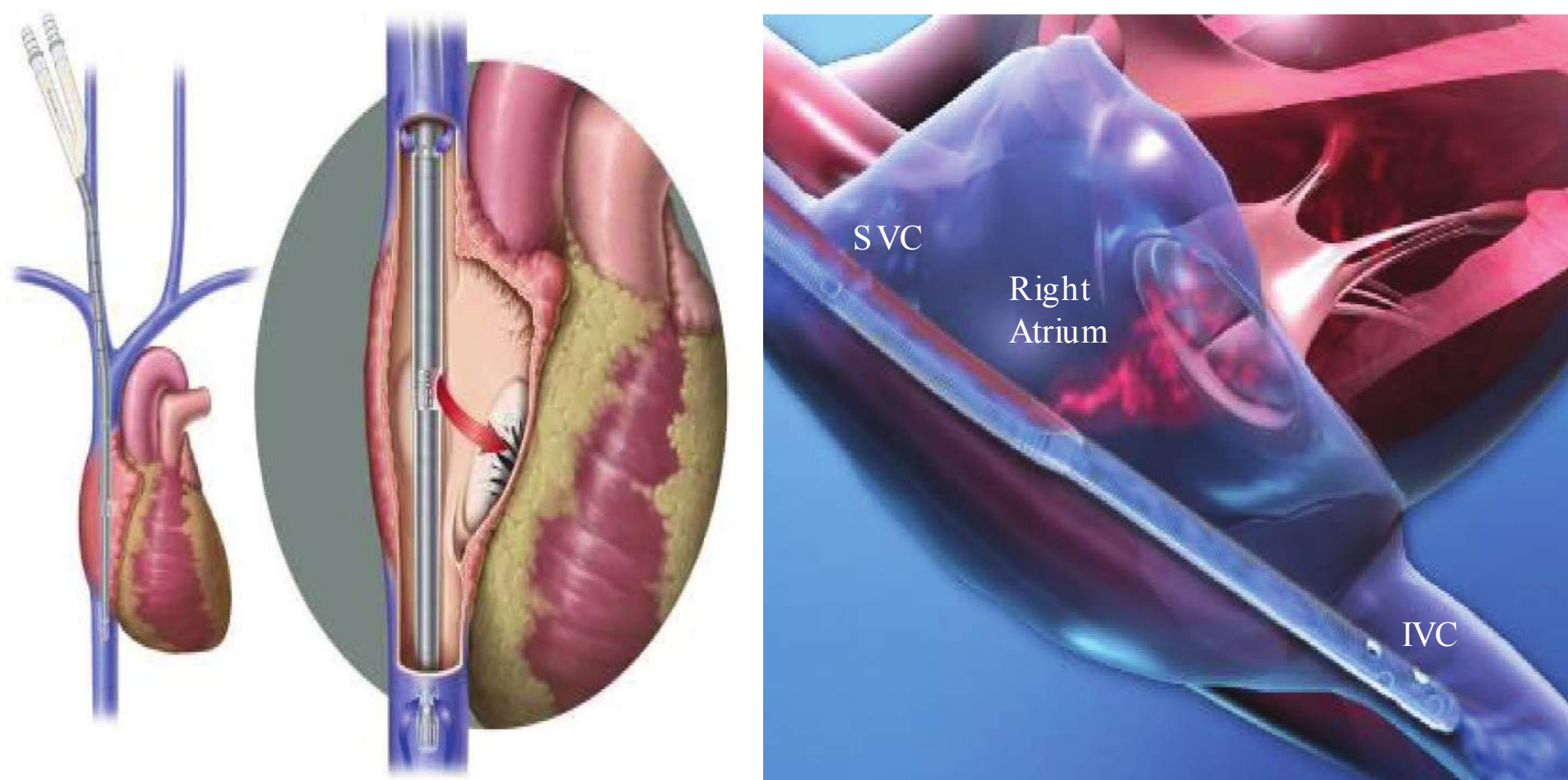


FIGURE 9-6 Dual-lumen ECMO cannulation via a percutaneous right jugular vein approach using the Avalon ELITE Bicaval Dual-Lumen Catheter®. Note the deoxygenated venous outflow into the cannula lumens in the superior vena cava and perihepatic inferior vena cava. A medial cannula lumen provides inflow of oxygenated venous blood directly into the right atrium. (Used with permission from Maquet Cardiopulmonary GmbH)

simultaneously removing blood from both the superior vena cava and inferior vena cava and returning blood to the right atrium. Dual-lumen VV-ECMO cannulation requires fluoroscopy for placement of the distal cannula tip into the perihepatic inferior vena cava for outflow, for positioning the medial inflow “arterial” lumen above the diaphragm (Figure 9-7), and to avoid the serious complication of right ventricular rupture.²⁸ By contrast, the bifemoral-jugular approach uses cannulae placed in both the superior vena cava and the inferior vena cava via the jugular and femoral veins, and returns oxygenated blood via the femoral vein to the right atrium.

The Circuit

When catheter access has been obtained, the patient is connected to the ECMO circuit. Often, the circuit may be primed with blood to avoid hypotension from acute changes in hemoglobin that can occur with crystalloid primed circuits. Venous blood is removed from the patient via the drainage catheter and pumped through an artificial lung called a membrane oxygenator. In the oxygenator, diffusion of oxygen occurs because of a pressure gradient between the partial pressure of oxygen in the patient’s venous blood being pumped through the circuit and the partial pressure of oxygen perfusing the membrane oxygenator.

Venous saturation (SvO_2 or $ScvO_2$) is used to assess the adequacy of oxygen delivery from the ECMO circuit. It is kept in the normal range (65%–75%). This is accomplished by titrating the ECMO circuit’s pump flow rate. Increasing the flow rate increases oxygen delivery and directly affects the venous saturation.

Carbon dioxide diffusion across the membrane is also a function of the diffusion gradient from the patient blood to the ECMO circuit gas, that is, the gas ventilating the membrane oxygenator. The $PaCO_2$ is adjusted by titrating

the amount of gas used to ventilate the oxygenator, termed “sweep gas.” Increasing the sweep will increase CO_2 removal and decrease $PaCO_2$, while decreasing the sweep will increase $PaCO_2$.

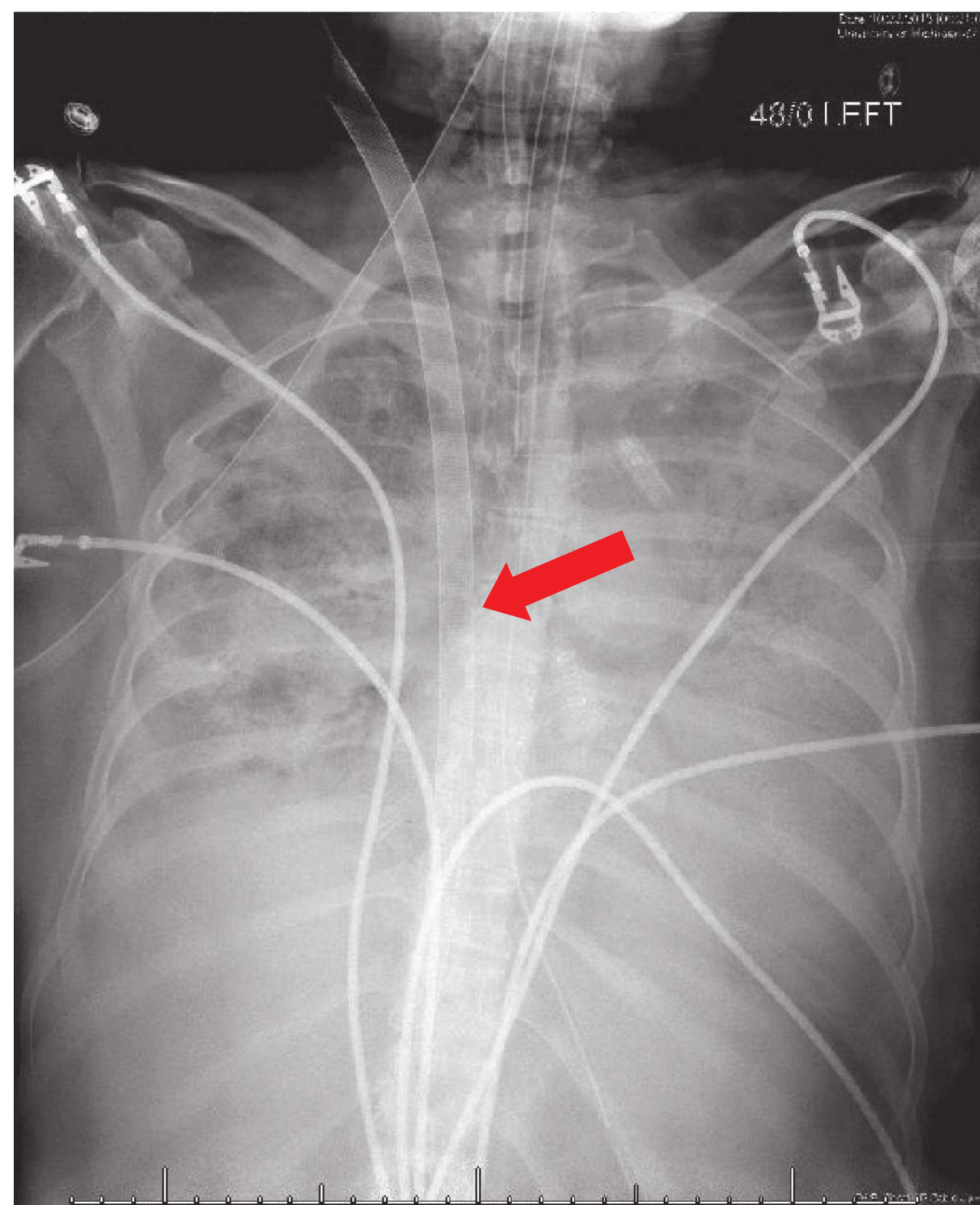


FIGURE 9-7 Optimal placement of 31 French Avalon Bicaval Dual-Lumen ECMO cannula for VV-ECMO: Distal tip in perihepatic inferior vena cava for venous outflow; medial inflow “arterial” lumen above diaphragm positioned medially (red arrow). (Used with permission from Lena Napolitano MD.)



TABLE 9-3: Summary of Differences Between VA-ECMO and VV-ECMO

Parameter	Venoarterial ECMO	Venovenous ECMO
PaO ₂	Higher PaO ₂ is achieved	Lower PaO ₂ is achieved
Perfusion rate	Lower perfusion rates are needed	Higher perfusion rates are needed
Pulmonary circulation	Bypasses pulmonary circulation Decreases pulmonary artery pressures	Maintains pulmonary blood flow Elevates mixed venous Po ₂
Affect on cardiac support	Provides cardiac support to assist systemic circulation	Does not provide cardiac support to assist systemic circulation
Cannulation system	Requires arterial cannulation	Requires only venous cannulation

Data from *the University of Michigan, Department of Surgery, Ann Arbor, Michigan.*

After being pumped through the oxygenator, the oxygenated blood, under pressure, is pumped through a heat exchanger that maintains the patient's body temperature at a set temperature, usually 37.0°C. The blood is pumped either to the arterial circulation via the aorta in VA-ECMO or back into the venous circulation via the right atrium in VV-ECMO.

Currently, ECMO circuits require the use of systemic anticoagulation with heparin to keep the system patent. The surfaces of the ECMO circuit and devices are plastic and therefore thrombogenic. It is necessary to provide anticoagulant prophylaxis to the patient's blood with a continuous infusion of heparin. The level of anticoagulation is measured by whole-blood activated clotting times (ACT, maintained approximately 180–240 seconds) or by aPTT or anti-Xa levels for adequate systemic anticoagulation.

Following ECMO initiation, ventilator settings are reduced to lung protective settings including low tidal volume (6 mL/kg), low plateau pressures (25 cm H₂O), and spontaneous breathing modes (to prevent diaphragmatic inactivity). These settings help avoid propagation of VILI. Higher PEEP during VV-ECMO is associated with a survival benefit.²⁹ Optimal mechanical ventilation settings during VV-ECMO still remain an area of controversy. Patients are also diuresed to dry weight.

Hemoglobin levels are kept above 10 g/dL and platelet counts above 100,000/mL; however, ECMO centers are moving toward more restrictive blood transfusion strategies to avoid transfusion-related complications. In the EOLIA trial, hemoglobin target is 7 g/dL and platelet target is greater than 50,000/mL. For a summary of differences between VA-ECMO and VV-ECMO, see Table 9-3.

ECMO COURSE AND WEANING

The average adult ECMO course can vary from days to weeks. During the first 24 to 48 hours, the condition of a patient's lungs may worsen as evidenced by increased radiographic opacification, which is thought to be due to the suddenly decreased airway pressure due to diversion of pulmonary flow by ECMO. Additionally, it is thought that various vasoreactive substances are released and activated from the patient's blood in reaction to the ECMO circuit surface. Improvement of lung function and compliance usually begin to occur within 1 to 3 days, but can also be significantly delayed.

As lung function improves, patients are weaned from ECMO by decreasing sweep and/or decreasing the circuit flow. When evidence of improved lung compliance and adequate gas exchange without excessive ventilatory support has been demonstrated, a weaning trial off ECMO is performed (sweep gas is disconnected but ECMO flow is maintained). Good indicators of lung recovery include improving chest radiographs, increasing lung compliance, increasing PaO₂, and decreasing PaCO₂ on rest ventilator settings. Prone position is commonly used during the ECMO weaning phase to recruit the posterior, dependent, atelectatic areas of the lung and achieve expanded alveolar recruitment to hasten native lung recovery (Figure 9-8).

Eventually, the patient is removed from ECMO support and the catheters are removed (decannulation). In VV-ECMO, if the femoral vein was cannulated, placement of an inferior vena cava filter should be considered, as insertion-site-related venous thrombosis is universal with femoral venous decannulation and inferior vena cava clot is common. This can be accomplished by use of intravascular ultrasound via the existing femoral venous ECMO cannula.³⁰ Systemic



FIGURE 9-8 Prone positioning is used during the VV-ECMO weaning phase to recruit posterior consolidated lung to promote native lung recovery. (Used with permission from Lena Napolitano MD.)

**TABLE 9-4: Mechanical Complications of ECMO**

Source of Complication	Nature of Complication
Cannula	Vascular injuries, limb ischemia, bleeding, compartment syndrome, limb amputation, pneumothorax, infection, emboli
ECMO circuit	Air emboli, thrombocytopenia, hypothermia, clot development (oxygenator failure, consumptive coagulopathy, pulmonary or systemic emboli)

Data from Van Meurs K, Lally KP, Peek G, Zwischenberger JB (2005) *ECMO: Extracorporeal Cardiopulmonary Support in Critical Care (The "Red Book")*, Third Edition. Michigan, Extracorporeal Life Support Organization.³

anticoagulation for 6 months should also be considered for prevention or treatment of deep venous thrombosis at the ECMO cannulation insertion sites.

COMPLICATIONS

As with any invasive procedure, ECMO has many potential life-threatening complications that can occur. These can be categorized into mechanical complications and patient complications (Tables 9-4 and 9-5). Mechanical complications are related to cannula placement and the ECMO circuit itself. Patient complications may be attributed to physiologic complications that occur due to ECMO therapy.

Mechanical Complications

The required placement of large-bore ECMO cannulae can cause several complications. As with placement of any type of central line, pneumothorax, line infection, and bleeding may occur. In addition, due to the larger size of the cannula required with ECMO, direct damage to the internal jugular vein can cause massive mediastinal bleeding. Cannulation of the carotid artery can cause dissection of the carotid arterial intima, leading to aortic dissection. In addition, any potential

for bleeding from the placement of the cannulae is increased due to the requirement of systemic heparinization to maintain the ECMO circuit. The cannulae may also serve as a nidus for thrombus formation and emboli.

The ECMO circuit has the potential to cause numerous complications. Because the surfaces of the ECMO circuit and devices are plastic, it is necessary to provide anticoagulant prophylaxis to the patient's blood with a continuous infusion of heparin. The most common mechanical complication is the development of clots within the circuit. These develop due to platelets adhering to the plastic surface of the circuit, becoming activated, recruiting more platelets, and growing into platelet aggregates. Eventually, these platelet aggregates break off. These clots can cause failure of the ECMO circuit's oxygenator. Larger clots can cause pulmonary or systemic emboli. Thrombocytopenia and a consumptive coagulopathy may also occur due to a large clot burden in the circuit.

Air can enter the ECMO circuit from dislodgment of a cannula (which then sucks in air), a small tear in the membrane oxygenator, compromised integrity in any of the connections in the circuit tubing, or high partial pressure of oxygen in the blood. Small bubbles in the circuit can be easily removed and have low potential for harm. A large bolus of air can be fatal.

Malfunction of the circuit heat exchanger can lead to significant patient hypothermia that may cause or exacerbate any coagulopathy that already exists.

Patient Complications

Patients undergoing ECMO therapy can suffer complications in any organ system.³¹ Many of these complications are due to the need for systemic anticoagulation.

Neurologically, patients may have spontaneous intracranial bleeding due to anticoagulation. This is more commonly seen in the neonatal ECMO population. Infarction from emboli may occur, and seizures induced by bleeding, infarction, or hypoxemia are also a threat.

Musculoskeletal complications occur due to femoral arterial cannulation with VA-ECMO. Significant vascular

**TABLE 9-5: Patient Complications of ECMO**

Systemic Source of Complication	Nature of Complication
Neurologic	Seizures, intracranial bleed, infarction, paralysis
Hematologic	Hemolysis, hemorrhage, coagulopathy, thrombocytopenia
Pulmonary	Pneumothorax, pulmonary hemorrhage
Metabolic	Acidosis/alkalosis, hyponatremia/hyponatremia, hypokalemia/hyperkalemia, hypoglycemia/hyperglycemia, hypocalcemia/hypercalcemia
Musculoskeletal	Limb ischemia, compartment syndrome
Renal	Acute tubular necrosis, oliguria
Cardiac	Myocardial stunning, pericardial tamponade
Gastrointestinal	Hemorrhage, biliary calculi, elevated direct hyperbilirubinemia

Data from Van Meurs K, Lally KP, Peek G, Zwischenberger JB (2005) *ECMO: Extracorporeal Cardiopulmonary Support in Critical Care (The "Red Book")*, Third Edition. Michigan, Extracorporeal Life Support Organization.³

compromise to the extremity in which the femoral catheter is placed may occur, resulting in limb ischemia, compartment syndrome, and even limb amputation. Pulses should be checked manually or using Doppler. Compartment syndrome should be suspected if swelling or tightness of the lower extremity is present and early consultation should be considered for potential fasciotomy.

Hemolysis from clot development typically manifests itself as renal dysfunction and rising serum haptoglobin levels. Coagulopathy and thrombocytopenia occur due to platelet consumption from activation by the circuit's plastic surface. Moreover, a dilutional coagulopathy can occur. Hemorrhage at any surgical site or cannula site, or into the site of previous invasive procedures is a frequent complication because of systemic heparinization. Intrathoracic, abdominal, or retroperitoneal hemorrhage may also occur. Exsanguination from circuit disruption, while uncommon, can be fatal.

Pericardial tamponade can occur due to cannula placement in the face of systemic anticoagulation. Myocardial stunning, which is defined as a decrease of left ventricular ejection fraction by more than 25%, may occur with the initiation of ECMO, requiring further VA-ECMO support or vasopressor and inotropic support. Fortunately, stunning is a temporary effect and cardiac ejection function typically returns to normal within 48 hours of ECMO initiation.

Pulmonary hemorrhage and spontaneous and iatrogenic pneumothorax may occur, as well. Oliguria is common during early ECMO therapy, and acute tubular necrosis and renal failure may occur from hemolysis, hypovolemia, or decreased perfusion.

Gastrointestinal hemorrhage may occur due to physiologic stress response, ischemia, embolism, or systemic anticoagulation. Elevated direct bilirubin and the development of biliary calculi occur secondary to prolonged fasting, use of parenteral nutrition, hemolysis, and diuretics. Last, due to the ECMO circuit functioning as a large intravascular foreign body, numerous metabolic complications may occur. Either acidosis or alkalosis and nearly any kind of electrolyte disturbance may develop.

Due to the highly invasive nature of ECMO and the potential for numerous complications, a trained ECMO technician is usually present continuously, 24 hours per day, at the patient's bedside to monitor the circuit and the patient for potential complications. This technician is in addition to the patient's usual nursing personnel.

PROLONGED ECMO AND FUTILITY

We are now recognizing that the lung has unexpected regenerative capacity during prolonged mechanical support, similar to acute kidney injury and native renal recovery.^{32,33} Newer data have confirmed that prolonged ECMO can still have favorable outcomes. A retrospective single-institution analysis of 127 patients from the ECMO Center in Regensburg, Germany reported no difference in survival for adult patients receiving VV-ECMO when comparing an ECMO

duration of 10 days or less (59%) versus a duration of greater than 21 days (52%).³⁴ A retrospective review of 3200 pediatric respiratory failure ECMO patients reported that 12% of all cases were prolonged (defined as > 21 days), which was associated with a 38% survival rate.³⁵

A recent retrospective review of multi-institutional data from the ELSO registry of adult patients (> 18 years old, n = 974) receiving ECMO from 1989 to 2013 for severe respiratory failure and requiring ECMO support for > 14 days reported that there has been an increasing prevalence of prolonged ECMO, with 72% of all cases reported since 2008.³⁶ Overall survival to discharge was 45.4% and did not vary with ECMO duration. Multivariate analysis confirmed that prolonged ECMO patients from 2007 to 2013 had a lower risk of death (odds ratio 0.65, 95% CI 0.45–0.92) compared with 1989 to 2006. Independent factors associated with survival were younger age and lower PaCO₂.

A number of studies have developed scoring systems to estimate survival probability in patients undergoing ECMO for severe ARDS, including the ECMOnet score,³⁷ PRESERVE score,³⁸ and RESP score.³⁹ All of these scores require future validation in prospective randomized clinical trials.

CONCLUSION

ECMO is an effective, cutting-edge technology capable of providing pulmonary and cardiac life support in select patients with severe respiratory failure. Often, these patients have a high mortality risk despite optimal conventional medical care. While ECMO treatment is not without its risks and complications, it is a reasonable treatment modality that will allow for the recovery of injured native lung and improved survival in a patient population with a previously poor predicted outcome.

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PULMONARY DISORDERS

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Acute Respiratory Failure

Imoigele P. Aisiku • Peter M.C. DeBlieux

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INTRODUCTION

The respiratory system primarily functions to provide adequate oxygenation and carbon dioxide elimination for the purposes of sustaining aerobic metabolism and pH homeostasis. Acute respiratory failure (ARF) is broadly defined as the inability to effectively manage gas exchange due to an impairment of the respiratory system. Although the etiologies of respiratory failure are too numerous to list, the underlying pathophysiologic mechanisms are similar and usually lead to a final common pathway. A consensus definition has not been established for ARF. Several large studies have defined severe ARF or acute respiratory distress syndrome (ARDS) as a $\text{PaO}_2/\text{FiO}_2$ ratio < 200 , or $\text{PaO}_2 < 60$ with either a FiO_2 of > 0.6 (hypoxemic) or a $\text{PaCO}_2 > 50$ (hypercapnic). ARDS recently has been redefined. The American European Consensus definition had been used since 1994 and was replaced with the Berlin definition in 2012^{1,2} (Table 10-1). Irrespective of the criterion used to establish ARF, it can generally be stated that all patients with respiratory impairment will have either primary ventilatory or primary oxygenation impairment (Figure 10-1).

ARF is one of the leading causes of admission to the intensive care unit (ICU). Incidence ranges for ARF, acute lung injury (ALI), and ARDS in adults were found to be 77.6–88.6, 17.9–34.0, and 12.6–28.0 cases/100,000 population per year, respectively.^{3,4} Mortality rates of approximately 40% were reported for patients with ARF, and similar or slightly lower rates for those with ALI and ARDS.^{5,6} A population based, pre-hospital study evaluated 19,858 cases for respiratory distress and found one-third of

those required intensive care admission. The most common discharge diagnoses for patients admitted to the hospital were congestive heart failure (CHF; 16%), pneumonia (15%), chronic obstructive pulmonary disease (COPD; 13%), and acute respiratory failure (13%).⁷

Physiologically, the respiratory system is composed of the lung and the respiratory pump. The respiratory pump consists of the chest wall, respiratory muscles, and the central nervous system innervations. Four types of respiratory failure are typically defined; they include Type I (hypoxemic), Type II (hypercapnic), Type III (peri-operative), and Type IV (shock) respiratory failure. Type I and II represent the majority and will be discussed in greater detail. Type III represents a combination of post-operative clinical scenarios including residual effects from anaesthesia, post-operative pain, and abnormal abdominal mechanisms from position, pain, obesity, or ascites that lead to progressive atelectasis. Type IV failure represents patients who have developed respiratory failure secondary to extrapulmonary sources such as cardiogenic, hypovolemic, and septic shock. In these instances, the primary goal is to unload the respiratory system and minimize oxygen consumption.

This chapter will discuss the basic pathophysiologic mechanisms of hypoxemic and hypercapnic respiratory failure and the approach to the management of these patients. The most common diseases for respiratory failure are discussed in other chapters and will not be discussed in great detail here. Cervical spinal cord injury (SCI) and neuromuscular diseases represent two disease processes that will be covered in greater detail here because they present their own unique challenges.

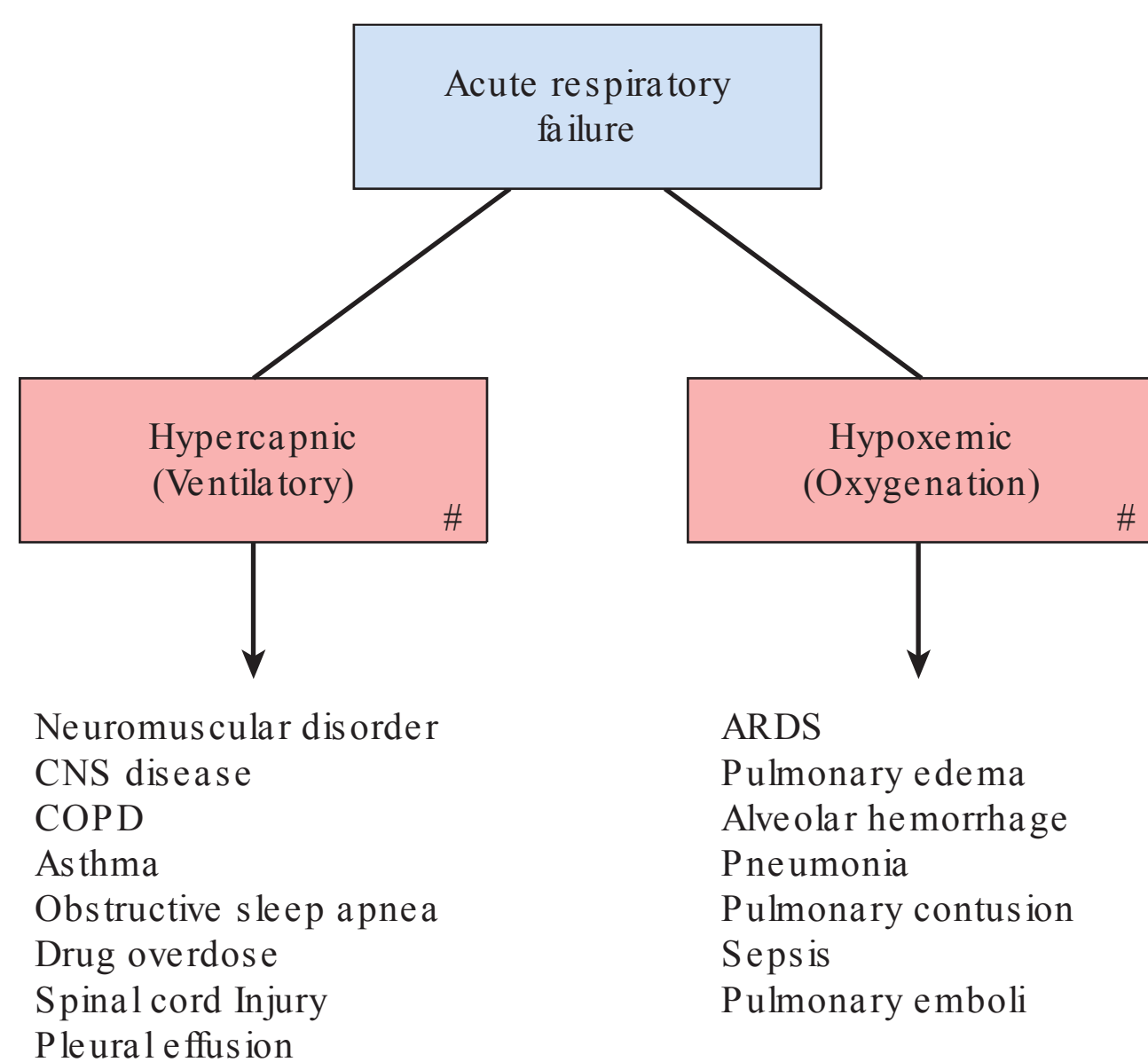

TABLE 10-1: Definition of ARDS: North American European Consensus Conference and Berlin Definition

AECC Definition	Berlin Definition
1. Acute onset	1. Acute onset within 7 days
2. Bilateral pulmonary infiltrates consistent with pulmonary edema	2. Bilateral pulmonary infiltrates consistent with pulmonary edema
3. Impaired oxygenation: $\text{PaO}_2/\text{FiO}_2$ ratio < 300 mm Hg \rightarrow ALI $\text{PaO}_2/\text{FiO}_2$ ratio < 200 mm Hg \rightarrow ARDS	3. Impaired oxygenation $\text{PaO}_2/\text{FiO}_2$ ratio 200–300 mm Hg \rightarrow mild $\text{PaO}_2/\text{FiO}_2$ ratio 100–200 mm Hg \rightarrow moderate $\text{PaO}_2/\text{FiO}_2$ ratio < 100 mm Hg \rightarrow severe
4. No evidence of left heart failure $\text{PAWP} \leq 18$	4. Impaired oxygenation not fully explained by cardiac failure

MECHANISMS OF RESPIRATORY FAILURE

Hypoventilation

Hypoventilation is a reduction in the volume of gas delivered to the alveoli per unit time (alveolar ventilation). Alveolar ventilation is clinically described in terms of minute ventilation. Minute ventilation is the total air volume that is expired in 1 minute and is calculated as the product of tidal volume and respiratory frequency. The clearance of CO_2 is a direct reflection of alveolar ventilation. Hypoventilation always causes a rise in the alveolar and arterial Pco_2 . The fall in Po_2 that accompanies hypoventilation can be estimated using the alveolar gas equation ($\text{PaO}_2 = \text{PIO}_2 - (\text{PaCO}_2/\text{R}) + \text{F}$, in which R = respiratory quotient, and F is the correction factor).



Some of these disorders have combined oxygenation & ventilatory pathophysiology

FIGURE 10-1 Common causes of acute respiratory failure in the ICU.

While this equation is not practical in the clinical environment, conceptually it demonstrates that in the setting of a normal respiratory quotient, the Po_2 decreases greater than the Pco_2 increases. Alveolar hypoventilation of a non-pulmonary etiology is typically characterized by hypercapnia with a normal alveolar–arterial oxygen gradient (A–a gradient) and therefore differs from the other three mechanisms of hypoxemia.⁸ Hypoventilation, or apnea, causes the partial pressure of alveolar oxygen to fall faster than the rise of the partial pressure of carbon dioxide. The other three mechanisms are typically characterized by a widening A–a gradient, which is normally less than 20 mm Hg.⁸ Hypoxemia secondary to hypoventilation is typically correctable with supplemental oxygen.

Diffusion

Diffusion typically refers to oxygen transport across the alveolar capillary membrane. In non-diseased states, oxygen transport is diffusion and perfusion limited. The diffusion properties of the alveolar membrane depend on its thickness and area. The diffusing capacity is reduced by diseases that thicken this membrane, including acute conditions such as pulmonary edema or chronic conditions that include diffuse interstitial pulmonary fibrosis, asbestosis, and sarcoidosis (Figure 10-2A). It is also reduced when the area is decreased, for example, by emphysema or pneumonectomy. Theoretically, impaired diffusion prevents complete equilibration of alveolar gas with pulmonary capillary blood. The clinical relevance of this is often questioned, since most transport is more perfusion limited than diffusion limited.

Shunt

The term shunt refers to the percentage of the total systemic venous blood flow that bypasses the gas-exchanging membrane of the lung and transfers venous blood unaltered to the systemic arterial system (Figure 10-2B). Shunting can be intracardiac, as in cyanotic right to left congenital heart disease, opening of a patent foramen ovale due to right ventricular overload, or result from passage of blood through pulmonary arteriovenous malformations. The most common cause of shunting is pulmonary disease.

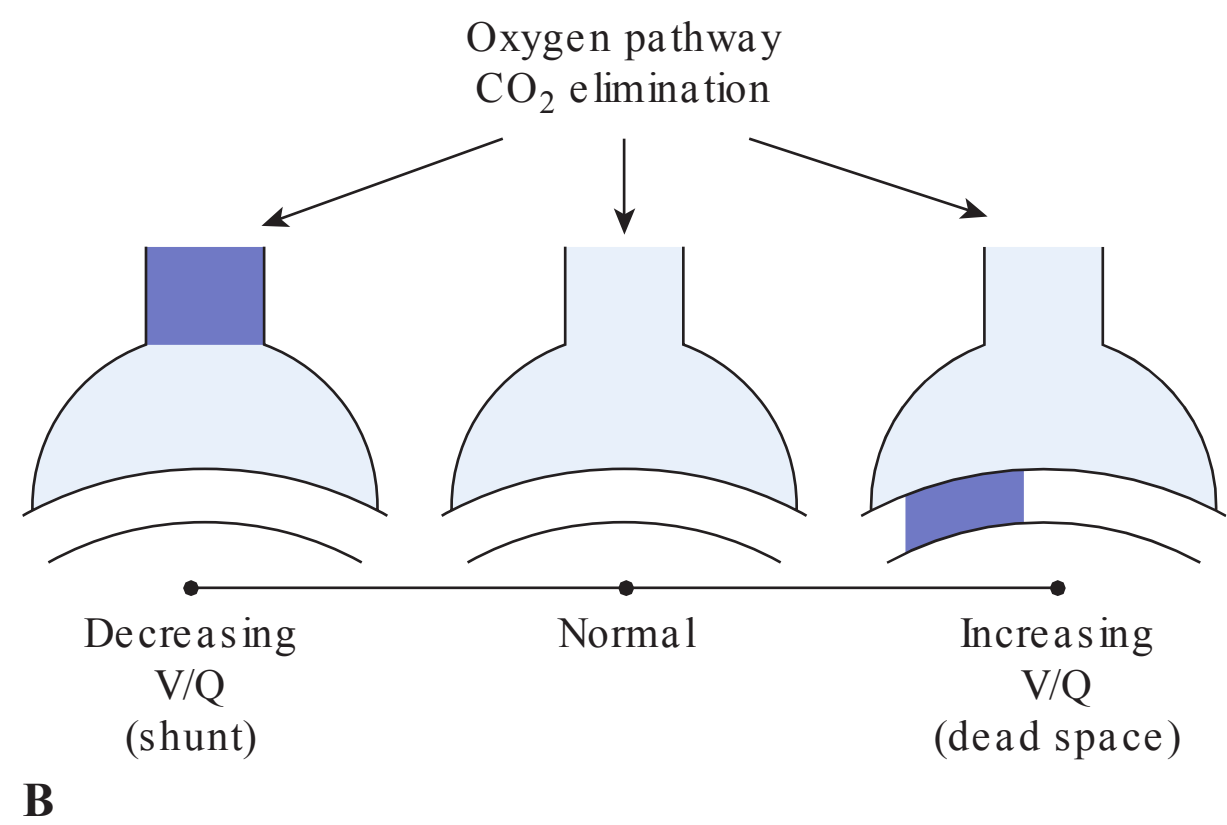
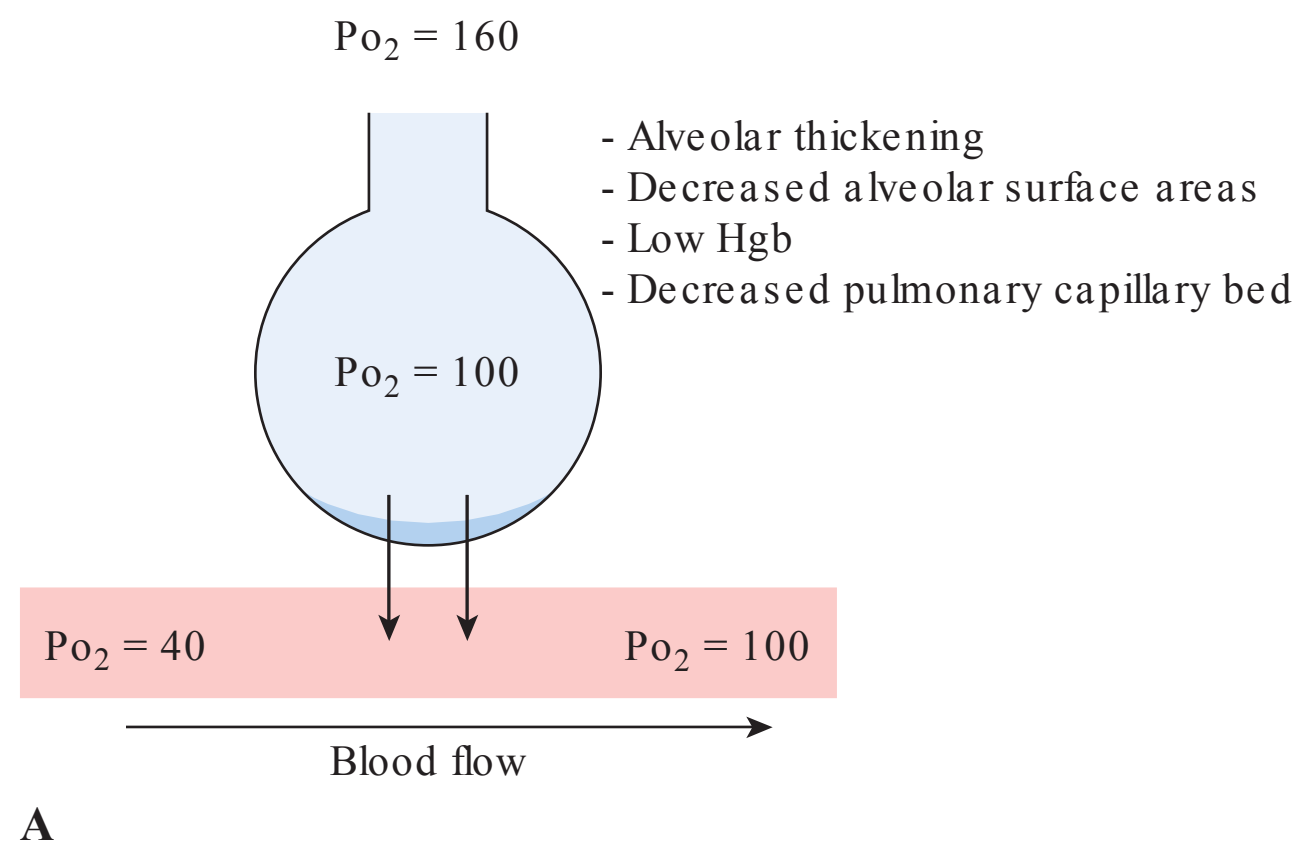


FIGURE 10-2 (A) Oxygen diffusion; (B) ventilation/perfusion mismatching.

In lung disease, there may be gas-exchanging units that are completely unventilated because of airway obstruction, atelectasis, or alveolar filling with fluid or cells. Hypoxemia caused by increased shunt, even small amounts of shunt, may lead to hypoxemia that may be refractory to supplemental oxygen. This is characteristically different from the other mechanisms (hypoventilation, diffusion, and V/Q mismatch) that may be more responsive to supplemental O₂.

Ventilation-Perfusion

Even in normal subjects, ventilation and perfusion in different areas of the lung are unequal, resulting in inefficient gas exchange (Figure 10-2B). This leads to V/Q mismatch. Areas of low ventilation relative to perfusion contribute to hypoxemia, are the most common cause of hypoxemia in lung disease, and an important cause of hypoxemia affecting patients in the ICU.

Even in normal subjects, the distribution of ventilation varies depending on the mode of ventilation and position. However, in non-pathologic disease states, ventilation is not uniform. The right lung is developmentally larger and receives greater ventilation. The position of the subject also influences ventilation, with the apices of both lungs receiving a greater percentage of ventilation than the bases in the upright position, while the lower lung is preferentially ventilated when lying in any horizontal position, irrespective of which side is dependent (supine, prone, or on a side). This is due to the dependent diaphragm lying higher in the thorax, with increased length of muscle fibers providing more efficient contraction during inspiration. In the sedated and paralyzed patient, the upper lung receives more gas flow.

The bases of both lungs receive more pulmonary blood flow than the apices in the erect subject. The distribution of flow through the lung is uneven due to the relatively low pressures in the pulmonary circulation, so gravity assumes a greater role than in the systemic circulation. While supine or prone, gravity assumes a more constant role throughout the lungs, though, in a lateral position, the dependent lung is perfused more than the upper lung.

Although both perfusion and ventilation increase from the apices to the bases in a subject lying horizontally, the increase

in ventilation is less than that of perfusion. The relationship between the two is described as the V/Q ratio. Resting values are approximately 4 L/min for ventilation and 5 L/min for pulmonary blood flow. This offers an overall ratio of 0.8 throughout the whole lung, assuming that ventilation and perfusion of all alveoli are equal.

V/Q mismatch is responsible for the hypoxemia seen in pulmonary edema, COPD, pulmonary embolism, and interstitial lung disease. The hypoxemia worsens with increasing V/Q mismatch for two reasons. First, with V/Q mismatch, a greater percentage of the cardiac output passes through lung units with lower V/Q ratios (perfusion > ventilation) so that less well-saturated blood makes a greater contribution to total pulmonary blood flow.⁹ Second, as mentioned previously in relation to shunts, the oxygen content of blood from lung units with low V/Q ratios exerts a greater effect on the saturation of blood flowing to the left side of the circulation because of the shape of the oxygen dissociation curve.⁹ Hypoxic pulmonary vasoconstriction (HPV) is a potent regulator of the distribution of blood flow to match areas of ventilation. It normally acts to improve gas exchange by reducing the blood flow to lung regions with low V/Q ratios. In conditions producing inflammatory mediators, such as sepsis and trauma, HPV is impaired, resulting in blood flowing to the poorly ventilated lung, causing hypoxia.⁹ Drugs such as sodium nitroprusside and nitroglycerine can impair HPV by indiscriminately causing vasodilation. HPV can also be abolished in the presence of raised pulmonary artery pressures, leading to V/Q mismatch and hypoxia.

HYPOXEMIC RESPIRATORY FAILURE

Hypoxemic respiratory failure is characterized by hypoxemia in the setting of normocapnia and represents primary failure of the lungs. Hypoxemic respiratory failure is usually the result of one or a combination of the four mechanisms described earlier including hypoventilation, alveolar oxygen diffusion abnormalities, shunting of systemic venous blood to the arterial circuit, or a V/Q mismatch. These descriptions

provide an accurate depiction of the physiologic mechanisms for hypoxemic respiratory failure and are useful in understanding how a particular disease causes hypoxemia.¹⁰

In a large multi-center, international, prospective cohort study of patients requiring mechanical ventilation (MV), the most common reported causes of ARF were post-operative respiratory failure, pneumonia, CHF, sepsis, and trauma.¹¹ In a small, prospective cohort study that included 41 patients with hypoxemic respiratory failure, COPD and pneumonia were the most common causes.¹² Other data from small, randomized controlled trials of noninvasive ventilation identified CHF, pneumonia, trauma, ARDS, and mucous plugging as the most common causes of respiratory failure.^{13,14}

HYPERCAPNIC RESPIRATORY FAILURE

Hypercapnic respiratory failure is characterized by hypoxemia and hypercapnia, representing failure of the respiratory pump. Alveolar ventilation becomes inadequate in relation to carbon dioxide production when either ventilatory demand exceeds the patient's capability (pump failure), or the patient's ventilatory effort is insufficient (drive failure).^{15–17} These two mechanisms are distinct in their clinical presentation. Alternatively, patients with acute failure of the ventilatory pump are dyspneic and tachypneic with other signs of distress and sympathetic nervous system activation, whereas patients with failure of ventilatory drive are not short of breath and typically demonstrate bradypnea or apnea.

Although acute ventilatory failure is primarily a disorder of alveolar ventilation, as demonstrated by increasing P_{CO_2} and decreasing pH, hypoxemia is usually present. More than one mechanism may coexist in a given patient at a given time, producing a life-threatening condition even when the individual processes are only moderate in severity.¹⁸ For example, in decompensated obesity hypoventilation syndrome, a patient whose underlying respiratory drive is reduced and whose obesity poses an increased elastic load on the ventilatory pump may develop acute-on-chronic ventilatory failure in the presence of a relatively modest increase in the work of breathing (WOB) from the additional restrictive effects of cardiomegaly and pleural effusions.¹⁹

In the ICU setting, the most common disorders encountered are:

1. Impairment of ventilatory drive due to sedative drugs;
2. Acquired neuromuscular disorders such as cervical SCI, Guillain–Barré syndrome (GBS), acute stroke, or amyotrophic lateral sclerosis (ALS);
3. Restrictive and obstructive diseases such as pulmonary fibrosis, chest wall burns, COPD, and asthma.

Cervical Spinal Cord Injury

Cervical SCI effectively disrupts the transmission of neurologic input from the respiratory centers to the ventilatory

muscles required for respiration. The diaphragm is innervated by the phrenic nerve whose root segments originate from C3–C5. Therefore, high cervical SCI may result in a permanent need for MV. Although patients with lower cervical SCI may initially require MV, successful rehabilitation could offer a ventilator-independent lifestyle.

The subacute management phase of cervical SCI may resemble that of most neuromuscular disease patients. The unique aspects are related to the acute management and the impact on the rehabilitation potential. Adverse physiologic effects of cervical SCI in the initial days or weeks after the injury include loss of lung volumes and inability to take deep breaths (which predisposes to atelectasis), inability to cough normally (which predisposes to the development of pneumonia and complicates its management), and impaired HPV (which predisposes to severe and often refractory hypoxemia when complicated by atelectasis or pneumonia). Retrospective studies have shown that both mortality²⁰ and ICU length of stay²¹ for patients with cervical SCI are more strongly influenced by the development of pneumonia and other respiratory complications than by the specific cord injury level.²²

In the un-intubated patient, initial management should include frequent assessment of forced vital capacity (FVC) and negative inspiratory forces (NIF). A vital capacity (VC) less than 1 L or an NIF > -20 (e.g., -10) despite normal blood gases and oxygenation warrants early intubation.

Ventilator management principles are different in these patients. Retrospective studies have demonstrated that high tidal volume ventilation or lung expansion ventilation may impact the duration of MV and decrease the incidence of atelectasis and pneumonia.²³ Contradictory to the lung-protective strategies of ARDS/ALI, patients are managed with tidal volumes of 15–20 cm³/kg while maintaining peak inspiratory pressures less than 40 cm H₂O. Exceptions to this mode of ventilation include severe traumatic brain injury, chest trauma, bilateral pulmonary contusions, flail chest, pneumothorax/hemothorax, or bullous emphysema. In a recent retrospective study, NIF and FVC were shown to be the best predictors of ventilator weaning in this patient population.²⁴

Neuromuscular Disorders

Patients with neurologic problems can develop respiratory failure from neuromuscular weakness, decreased central respiratory drive, or associated pulmonary complications. In patients with neuromuscular disease, respiratory failure can present as a consequence of the natural progression of a chronic condition such as ALS, exacerbation of a fluctuating disorder such as myasthenia gravis (MG), or sudden onset and fulminant course of an acute illness such as GBS.²⁵ In such cases, respiratory failure can result from worsening weakness affecting respiratory muscles or from an intercurrent pulmonary complication, typically aspiration.

GBS is the leading cause of non-traumatic acute paralysis in industrialized countries.²⁶ About 30% of the patients

have respiratory failure requiring ICU admission and invasive MV.²⁷ The underlying mechanism is progressive weakness of both the inspiratory and expiratory command systems. Several factors, if present either at admission or during the patient's hospital stay, predict a need for invasive MV. These factors include rapidly progressive motor weakness, involvement of both the peripheral limb and the axial muscles, ineffective cough, bulbar muscle weakness (dysarthria, dysphagia, impaired gag reflex), or a rapid drop in VC or respiratory pressures.²⁸

Upper airway muscle dysfunction is related to cranial nerve involvement and deserves special attention because impaired coughing is common and increases the risk of aspiration and aspiration-related complications such as atelectasis and pneumonia. Most commonly, the seventh, ninth and tenth cranial nerves are involved, manifesting as facial paralysis and swallowing impairment, respectively.^{29,30} If present, tongue weakness may contribute to the development of respiratory failure by causing upper airway obstruction during sleep, and aspiration during the initial phase of swallowing.³¹ The result is a combination of inadequate neuromuscular strength leading to alveolar hypoventilation, low tidal volume breathing, and diffuse atelectasis.

MV is frequently required when VC falls below 4–5 mL/kg ideal body weight and there is progressive worsening of bulbar functions.^{32,33} Therefore, patients with neuromuscular respiratory failure should be closely monitored with frequent measurements of VC, NIF, arterial blood gases, clinical evaluation of swallowing mechanisms, ability to handle secretions, and presence and strength of cough mechanism.

APPROACH TO THE PATIENT WITH ARF

As with all aspects of acute management of patients, airway, breathing, and circulation should be addressed. After assessing and securing the airway if necessary, the next step is to manage and diagnose the etiology of the respiratory failure. If intubating is not emergently required, evaluation continues with a high clinical suspicion for impending respiratory failure. Early recognition allows for greater therapeutic options.

The WOB in normal resting state accounts for approximately 5% of oxygen consumption and dramatically increases in diseased states. Although an oversimplification, WOB typically constitutes airway resistance and chest wall and lung compliance. Airway resistance is a function of airway caliber and flow. Compliance is the change in pressure over volume and encompasses the compliance of both the lungs and chest wall. Therefore, WOB is comprised of the amount of work necessary to overcome resistance of the airways (Figure 10-3) and the elastic recoil of the lungs and chest wall.

Signs of increased WOB include dysconjugate breathing, accessory muscle use, and tachypnea. These signs are compensatory mechanisms and often exist prior to oxygen desaturation. Systemic signs and symptoms that accompany an increased WOB include restlessness, anxiety, diaphoresis, confusion, seizures, somnolence, tachycardia, bradycardia,

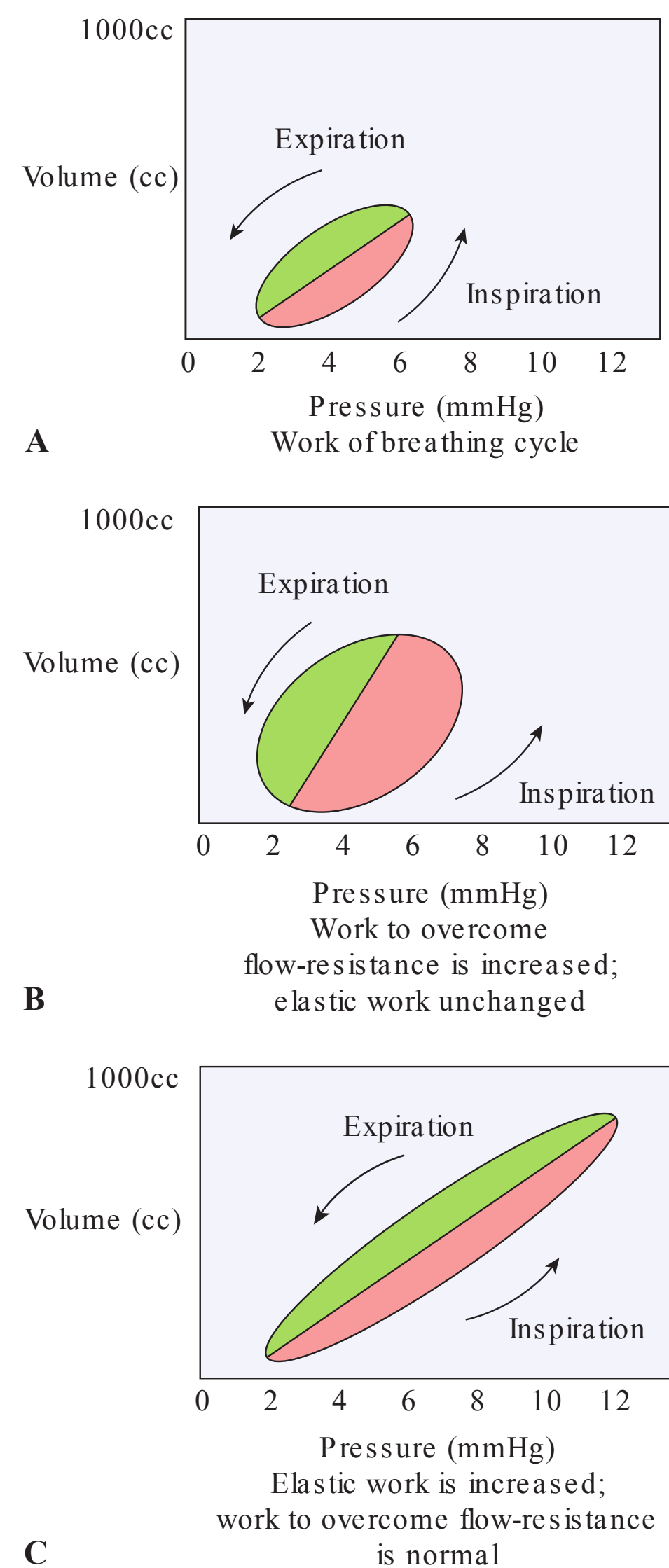


FIGURE 10-3 Work of breathing (pressure–volume diagram during one respiratory cycle). (A) Normal; (B) obstructive lung disease; (C) restrictive lung disease.

and arrhythmias. The key is to suspect and treat the increased WOB prior to the appearance of systemic signs and symptoms.

The goal of managing respiratory failure is to reduce the workload on the pulmonary system while the underlying etiology is resolved. The practitioner must consider early the possibility of respiratory failure. A common pitfall is to treat the signs and symptoms and miss the underlying etiology until full respiratory failure has ensued, and MV has become the only treatment option.

Once the respiratory distress/failure has been addressed, the next step is to evaluate the underlying etiology of the respiratory failure through the use of diagnostic aids. An arterial blood gas (ABG) and a chest x-ray should be the first diagnostic step in addressing a patient in respiratory distress. The ABG (Figure 10-4) and chest X-ray will provide important data as

Etiology	pH	PaCO ₂	PaO ₂	PAO ₂ - PaO ₂
Central nervous system	↓	↑	nl or ↓	nl or ↑
Peripheral nervous system	↓	↑	nl or ↓	nl or ↑
Asthma*	↑	↓	nl	↑
COPD#	↓	↑↑	↓↓	↑
Pneumonia**	↑	↓	↓↓	↑↑

*Early phase, pH & PaCO₂ may normalize as severity increases, which is ominous

Acute on chronic exacerbation

** Early in course before ventilatory failure

FIGURE 10-4 Arterial blood gas analysis in acute respiratory failure.

to the potential etiology for respiratory failure. It will distinguish between a primary oxygenation problem (widened A–a gradient), a primary ventilator problem (elevated Pco₂ and acidemia), or a combination of both. As respiratory failure ensues and progresses, the picture becomes mixed, particularly in the critically ill patient.

Treatment Options

ARF of hypoxemic nature can be addressed with MV, although this technology may not be necessary. It is common for practitioners to resolve ARF with non-invasive positive pressure ventilation (NPPV) or conventional MV. Securing the airway and initiating MV has significant risks and complications, and prolonged MV increases the incidence of ventilator-associated pneumonia, critical illness polyneuropathy, and ICU morbidity and mortality.

If the patient's condition allows sufficient time, attempts should be made to maximize all medical options before considering intubation. Supplemental oxygen therapy should be maximized. Supplemental oxygen in excess of 70% fractional inspired oxygen can be provided without the use of a ventilator. Nasal cannula, Venturi mask, partial non-rebreather, non-rebreather, and complex air entrainment high-flow systems can be set up to deliver high FiO₂. In instances in which airway resistance is increased, such as COPD or asthma, or in upper airway obstructive scenarios, such as post-extubation stridor, heliox (70:30 or 80:20 mixtures) may facilitate delivery of supplemental oxygen.³¹ Heliox is resource intensive and requires a significant amount of time to set up as well as continuous monitoring for respiratory improvement. The decision to use heliox should be made early in the evaluation and with preparation for the next therapeutic modality should the patient fail. The evidence for the successful utilization of heliox in the acute respiratory distress environment is limited.

Progressive hypoxic failure will lead to ventilatory failure secondary to fatigue. ARF of a primary ventilator disorder may be managed with close observation in the ICU and NPPV. NPPV has the advantage of improving tidal volume and minute ventilation while delivering high FiO₂, and may be of limited use in some neuromuscular disorders. Relative contraindications to NPPV include decreased mental status, hemodynamic instability, facial trauma or burns, abdominal process, inability to protect airway, and inability to clear

secretions. There is evidence to support the use of NPPV in certain disease states including COPD,³⁴ asthma,³⁵ pulmonary edema,³⁶ and post-operative respiratory failure.^{37,38}

When there is concern for the patient's ability to maintain his or her airway, the primary objective is to protect and maintain the airway, and traditional endotracheal intubation and conventional MV should be employed. The timing of intubation for airway protection purposes can be challenging. The decision to intubate and provide MV should not be the first treatment option and should never be needlessly delayed. MV should always be regarded as a temporizing measure while the underlying cause of respiratory failure is addressed. The keys to successful management of ARF are:

1. Ensure that the airway is secure;
2. Relieve the increased WOB;
3. Reverse the hypoxemia/hypercapnia;
4. Identify and treat the underlying disorder.

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Acute Respiratory Distress Syndrome (ARDS)

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DIAGNOSIS

The acute respiratory distress syndrome (ARDS), first identified by Ashbaugh et al. in 1967, described a constellation of findings in 12 patients who had experienced acute onset of tachypnea, hypoxemia, loss of lung compliance, cyanosis refractory to oxygen therapy, and diffuse alveolar infiltration on chest radiograph. Pathologic examination from seven of these patients found atelectasis, vascular congestion with hemorrhage, hyaline membranes, and pulmonary edema.¹

The initial description by Ashbaugh et al. provided vague criteria for diagnosis and was not specific enough to exclude other conditions. In 1988, Murray et al. developed a 4 point lung injury scoring system in an effort to better define the syndrome using specific and measurable criteria. The components of the score included alveolar consolidation measured by chest radiograph, hypoxemia measured by $\text{PaO}_2/\text{FiO}_2$ ratios, levels of required positive end-expiratory pressure (PEEP), and pulmonary compliance.²

In 1994, the American–European Consensus Committee (AECC) on ARDS implemented new criteria for the diagnosis of ARDS. It allowed for those with less severe hypoxemia to be classified as having acute lung injury (ALI) and those with more severe hypoxemia to be defined as having ARDS. The AECC defined ALI as the acute onset of respiratory distress with $\text{PaO}_2/\text{FiO}_2 < 300$ mm Hg, bilateral, patchy infiltrates on chest radiograph, and a pulmonary artery occlusion pressure (PAOP) < 18 mm or absent clinical evidence of left

atrial hypertension (indicating presumptive non-cardiac etiology of pulmonary edema). ARDS was given similar diagnostic criteria, but with $\text{PaO}_2/\text{FiO}_2 < 200$ mm Hg.³ The AECC definition of ARDS resulted in advancement in clinical and epidemiologic data, thereby improvements in care for patients with ARDS. However, after nearly two decades of use, a number of limitations with the AECC criteria persisted. In order to address these limitations, an international panel of experts convened in 2011 and developed the Berlin Definition of ARDS.⁴

The Berlin Definition of ARDS defined the term acute, eliminated the term ALI, and stratified ARDS into mild, moderate and severe based on the degree of hypoxemia by $\text{PaO}_2:\text{FiO}_2$ ratios. The definition requires a minimal PEEP of ≥ 5 cm H_2O , clarifies the radiographic criteria, and removes the PAWP requirement and defined risk factors (Table 11-1). This new definition was retrospectively evaluated against 3670 individuals from 4 multicenter randomized control trials (RCTs), 269 patients from 3 single-center trials and against the AECC definition. Retrospective analysis showed increasing mortality associated with severity and increasing median duration of mechanical ventilation (MV) with increasing severity.⁴

Pathologic examination is perhaps the gold standard for the diagnosis of ARDS with the key histologic finding being diffuse alveolar damage (DAD).⁵ While not typically performed to diagnose ARDS, one retrospective study concluded that open lung biopsy may be safely done for the diagnosis of ARDS, and in many cases (60% in their series) it produced



TABLE 11-1: The Berlin Definition of Acute Respiratory Distress Syndrome

Acute Respiratory Distress Syndrome	
Timing	Within 1 week of a known clinical insult or new or worsening respiratory symptoms
Chest imaging ^a	Bilateral opacities—not fully explained by effusions, lobar/lung collapse, or nodules
Origin of edema	Respiratory failure not fully explained by cardiac failure or fluid overload Need objective assessment (e.g., echocardiography) to exclude hydrostatic edema if no risk factor present
Oxygenation ^b	
Mild	200 mm Hg < PaO ₂ /FiO ₂ ≤ 300 mm Hg with PEEP or CPAP > 5 cm H ₂ O ^c
Moderate	100 mm Hg < PaO ₂ /FiO ₂ ≤ 200 mm Hg with PEEP ≥ 5 cm H ₂ O
Severe	PaO ₂ /FiO ₂ ≤ 100 mm Hg with PEEP ≥ 5 cm H ₂ O

Abbreviations: CPAP, continuous positive airway pressure; FiO₂, fraction of inspired oxygen; PaO₂, partial pressure of arterial oxygen; PEEP, positive end-expiratory pressure.

^aChest radiograph or computed tomography scan.

^bIf altitude is higher than 1000 m, the correction factor should be calculated as follows: [PaO₂/FiO₂ × (barometric pressure/760)].

^cThis may be delivered noninvasively in the mild acute respiratory distress syndrome group.

alternative diagnoses such as pneumonia, pulmonary hemorrhage, and interstitial fibrosis.⁶ Another retrospective study which evaluated for the presence of DAD on autopsy in those who met clinical criteria for ARDS using the Berlin definition found that only 45% had DAD on autopsy. The rate of DAD increased from 12%, 40%, and 58% with mild, moderate and severe ARDS, respectively. Using DAD as the standard, the Berlin definition was found to have 89% sensitivity and 63% specificity.⁷ This sensitivity and specificity is slightly improved from a previous autopsy study using the AECC definition, which had a sensitivity of 83% and specificity of 51%.⁸

Efforts are ongoing to identify biomarkers from serum or bronchial alveolar lavage fluid in ARDS. Such a biomarker may assist in identifying groups of patients with similar underlying pathophysiology. Numerous proteins, cytokines, and inflammatory markers have been investigated; however, none has yet to be validated in ARDS.⁹

Achieving diagnostic accuracy using clinical definitions is imperative so as not to underdiagnose or overdiagnose the pathology and to assure that clinical trials and treatment modalities are in fact targeting the correct disease process.

PATHOPHYSIOLOGY

ARDS describes a hypoxemic state that results from pulmonary edema secondary to damage to the alveolar or capillary endothelium. The pathophysiology is complex, mediated by multiple cell types and many cytokines, ultimately resulting in damage to and increased permeability of the alveolar capillary membrane (ACM). The ACM consists of the capillary endothelium and alveolar epithelium. The alveolar epithelium is made up of type 1 and type 2 alveolar epithelial cells. Type 1 cells make up roughly 90% of the alveolar epithelium and allow for gas exchange from the vascular endothelium. Type 2 cells produce surfactant, differentiate into type 1 cells and play a role in the resorption of fluid from the alveolar space.¹⁰

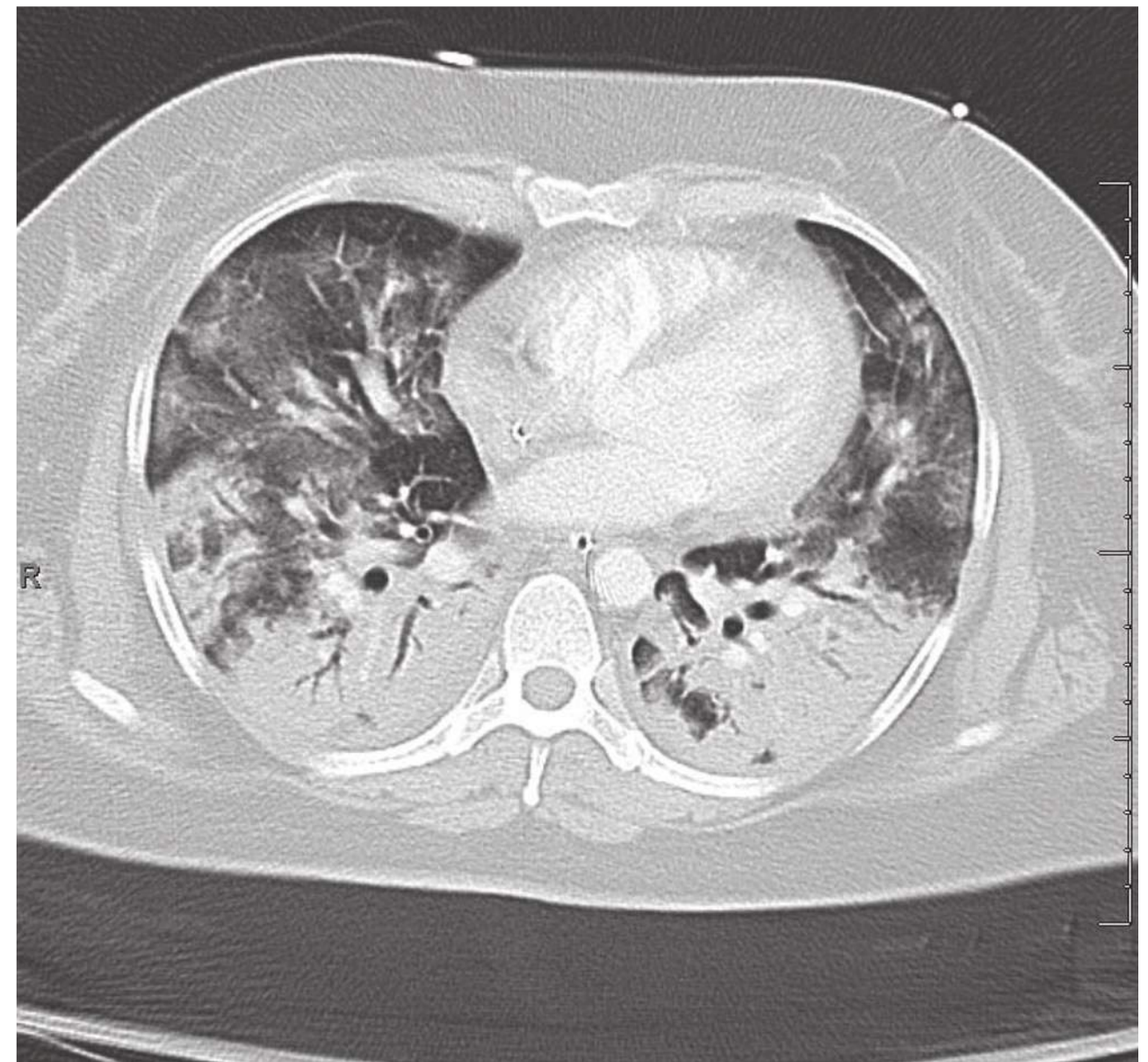
In ARDS, the ACM is activated by cytokines (tumor necrosis factor, IL-1, IL-6, and others) resulting in increased permeability. The increased permeability results in protein-rich fluid accumulation in the alveoli, which causes DAD. The DAD results in replacement of alveolar epithelial cells with hyaline membranes. Damaged type 1 cells result in impaired gas exchange. Damaged type 2 cells impair fluid resorption, which leads to exacerbation of pulmonary edema, and decreased surfactant production results in decreased compliance and alveolar collapse.

Two phases are described in ARDS. The acute or exudative phase is clinically characterized by rapid-onset respiratory failure and hypoxemia often refractory to supplemental oxygen. The chest radiograph during this phase typically reveals bilateral patchy infiltrates (Figure 11-1A) and computed tomography (CT) further elucidates increased density within the dependent lung zones (Figure 11-1B).¹⁰ Pathologic examination during this stage reveals DAD characterized by a disruption of the alveolar epithelium, capillary injury, microvascular thrombi, and the presence of inflammatory cells within the alveoli.

ARDS may completely resolve after the acute or exudative phase. However, a subset of patients progress with persistent hypoxemia, increased alveolar dead space with continued ventilation/perfusion mismatch, and, ultimately, fibrosing alveolitis. This fibroproliferative phase occurs 5–7 days after the onset of ARDS and begins after resolution of the acute exudative phase.¹¹ Progression to fibrosing alveolitis is also associated with a higher mortality rate.⁶ CT findings during this phase reveal reticular opacities, diffuse ground glass opacities, and bullae.¹⁰ Eventually, type 2 pneumocytes begin resorption of pulmonary edema and organize the hyaline membranes. They also repair the alveolar epithelium and differentiate into type 1 pneumocytes. With this repair comes interstitial pulmonary fibrosis with permanent disruption of the normal alveolar architecture.



A



B

FIGURE 11-1 **A.** Chest radiograph demonstrates diffuse alveolar infiltrates of ARDS. **B.** On CT, diffuse alveolar infiltrates with predominance in the dependent lung zones can be seen.

Iatrogenic injury from mechanical ventilation is a critical component which contributes to pulmonary inflammation in ARDS. Ventilator-induced lung injury (VILI) describes the microscopic and macroscopic pulmonary sequelae of MV.¹² VILI can be explained in terms of stress and strain. Strain is the change in shape or size of the lung (tidal volume/end expiratory lung volume) and lung parenchymal stress is the amount of force being exerted to cause the strain (transpulmonary pressure). In a healthy lung, the amount of stress required to distend the lung is relatively homogeneous. In a collapsed or damaged lung, the amount of stress required to cause strain in a lung region will depend on characteristics of those damaged or collapsed areas creating increased stress to distend collapsed segments the overdistention of opened alveoli and release of inflammatory cytokines that worsen capillary leak and alveolar edema, as described earlier. VILI has led to research in lung-protective ventilatory strategies that seek to limit the excessive stress applied to lung regions.

INCIDENCE/RISK FACTORS

The initial estimated incidence of ARDS by the National Heart and Lung Institute in 1972 was 75 per 100,000 person years in the United States.³ Epidemiologic studies since 1972 estimate the incidence at 13.5–58.7 per 10⁵ person-years.⁵ The incidence of ARDS has remained substantially unchanged over the last decade, resulting in approximately 200,000 new cases each year in the United States, and accounts for between 10–15% of all ICU admissions.¹³

Risk factors for ARDS are numerous and divided into direct and indirect (extrapulmonary), depending on their

mode of injury to the lung. Direct causes include aspiration, pneumonia, near drowning, toxic inhalation, trauma to the lung, and fat or amniotic fluid emboli. Indirect causes include sepsis, severe systemic trauma, blood product transfusion, drug overdose, acute pancreatitis, cardiopulmonary bypass, and disseminated intravascular coagulation. The most common risk factors of ARDS include direct lung injury, sepsis, and multiple blood product transfusions.¹⁴

Other predisposing conditions include renal transplant and alcoholism. It has been hypothesized that renal transplantation increases the risk for ARDS secondary to immunosuppression, which increases the risk for developing pneumonia and sepsis; however, similar associations were not found for recipients of liver or pancreas transplants.¹³ Similarly, alcoholism has been linked to increased susceptibility to ARDS; however, this association may be due to the increased predisposition of this population to trauma, aspiration pneumonia, sepsis and blood product transfusion from gastrointestinal bleeding.

Last, studies suggest a possible genetic susceptibility to ARDS along with other demographic factors (age, sex, and race), which further influence the risk of developing the disease and the resultant mortality.¹⁰

MORTALITY/PROGNOSIS

Only 9% to 16% of deaths from ARDS are the result of respiratory failure and hypoxemia. The most common cause of death is multiple organ failure and sepsis.¹⁵

Mortality in patients with ARDS was about 70% for the first decade after it was initially described and steadily decreased until 1994; since then, mortality has remained stable, between

36% and 44%.¹⁶ The most common predictors of mortality are advanced age, presence of nonpulmonary organ dysfunction, ongoing sepsis, shock, hepatic failure, degree of lung damage, and blood transfusion. There does not appear to be a mortality difference between direct pulmonary and indirect pulmonary causes of ARDS.¹⁰

Patients who survive ARDS often have cognitive, psychiatric and physical impairments. Estimates of cognitive dysfunction range from 30 to 55%. These rates are similar to those reported in survivors of critical illness in general. Depression, anxiety and posttraumatic stress disorder are commonly reported psychiatric disorders with rates of 36%, 62%, and 39%, respectively. Survivors of ARDS appear to regain pulmonary function within 12 months from ICU discharge, but with measurable functional disability.

An evaluation of 109 ARDS survivors at 1 year found them to have mild restrictive lung disease on pulmonary function testing. None of these patients required the use of supplemental oxygen at 12 months and only 6% of patients had arterial oxygen saturations below 88% with exercise.¹⁷ Yet, at 1 year from ICU discharge, only 49% of patients had returned to work, and quality of life assessments were below average. Interestingly, the functional limitations experienced were largely a consequence of persistent neuromuscular weakness and muscle wasting and, to a lesser extent, their persistent pulmonary dysfunction.

ARDS TREATMENT

As the etiologies and contributing factors to the development of ARDS are diverse, so are the approaches to supportive care and directed treatment of the lung-injured patient. The following section reviews treatment strategies supported by varying levels of evidence. Some strategies such as protective ventilatory strategies are supported by class 1 evidence, while others such as steroid therapy are still hotly debated. Because of the heterogeneous nature of critically ill patients as well as the heterogeneity of lung injury itself, the limitations of outcome studies using mortality endpoints must be recognized. Even the most well-done studies of ventilatory and pharmacologic strategies are impacted by many variables such as patient selection, etiology of lung injury, timing of therapy, and concomitant treatments. Thus, it is important to recognize strategies that are not supported by class 1 evidence, but may play a key role in the treatment of ARDS when considered within the context of the individualized care of the lung-injured patient.

SUPPORTIVE SYSTEMIC CARE

The importance of supportive critical care in the treatment of ARDS cannot be overstated. For example, a fluid-restrictive strategy (discussed later) has been shown to improve ARDS outcomes but would likely be harmful if this diverted attention from a targeted resuscitation to minimize the patient's degree of shock. The benefits of proven ventilatory strategies will be unrealized if appropriate treatment of infections is

not delivered, and even best practices regarding MV will not limit ventilator days without judicious use of sedatives, blood product transfusions, and nutritional supplementation.

Supportive care starts with treatment of the predisposing disease process. Advances in the care of these pulmonary and extrapulmonary conditions are responsible for the decreasing ARDS mortality over the years.¹⁸ Best care practices for sepsis, trauma, and other predisposing conditions must be followed if ARDS outcomes are to be optimized. ARDS is rarely an isolated organ system failure in ICU patients and mortality is more often associated with the accompanying multiorgan dysfunction syndrome.¹⁹ Thus, it is unlikely that any lung-directed treatment on its own will impact outcome without care directed to the cardiovascular, renal, and central nervous systems, as well.

FLUID AND HEMODYNAMIC MANAGEMENT

Optimization of hemodynamics and intravascular volume in ARDS is a challenging task. Since patient survival is directly related to extrapulmonary organ function, the overriding goal is to reverse shock and optimize organ perfusion while minimizing volume overload. Under-resuscitation potentiates ongoing hypoperfusion, which contributes to the inflammatory cascade and worsening lung injury. Conversely, once resuscitated, a fluid-restrictive strategy has been shown to improve pulmonary function in patients with ARDS.²⁰ The ARDS Clinical Trials Network performed a prospective randomized trial of a fluid-restrictive strategy versus a liberal fluid strategy in ventilated patients with ARDS.

They found that targeting lower filling pressures (central venous pressure [CVP] and PAOP) and tolerating lower urine outputs in the study group significantly lowered the amount of fluids administered and in turn improved oxygenation indices and lung injury scores, and minimized ventilator and ICU days as compared with control subjects. In this study, the fluid-restricted patients did not suffer any increased incidence of cardiovascular or renal dysfunction, although they did not realize any mortality benefit either. Similar conclusions were reached in a separate post hoc analysis of the surgical patient cohort from the larger trial. Hence, the paradigm of care is to first ensure that patients are resuscitated to the point of optimal organ perfusion and reversal of any shock state, but to not over-resuscitate them, as restricting further fluids and decreasing the overall hydrostatic pressure will lead to net negative fluid balances and improved pulmonary outcomes.

Another ALI treatment strategy with similar goals—using albumin repletion to increase colloid osmotic pressure in hypoproteinemic patients combined with furosemide diuresis to decrease hydrostatic pressure—has shown promise.^{21,22} Martin et al. evaluated this furosemide plus albumin regimen in a randomized, placebo-controlled trial and found improved oxygenation while reducing hypotension and shock, as compared with furosemide monotherapy.²² While the exact mechanisms require further elucidation, the authors

contend that the addition of albumin to a diuretic strategy stabilizes hemodynamics—presumably through the maintenance of effective circulating blood volume—while promoting egress of pulmonary edema fluid from the alveolar space.

Of course, even if one subscribes to a particular endpoint of fluid therapy (drier vs. wetter), targeting that endpoint of intravascular fluid repletion is no easy task. Since the general parameters of intravascular volume status such as urine output, heart rate, and blood pressure do not accurately predict volume responsiveness, clinicians have advocated for other hemodynamic monitoring tools to better titrate fluid therapy. The use of pulmonary artery catheters (PACs), for example, is the source of continuous debate, and their efficacy in guiding treatment in the ALI patient has recently been evaluated. The recent ARDS network trial of 1,000 ALI patients concluded that PAC-guided therapy did not improve survival or organ function, but was associated with more complications than central venous catheter (CVC)–guided therapy.²⁰ Others further argue that both the PAOP and the CVP are confounded by too many variables for these static filling pressures to be useful guides of volume therapy and that functional hemodynamic parameters are more accurate and preferable.

A growing body of literature supports the use, during MV, of dynamic arterial waveform-derived parameters—such as stroke volume variation (SVV) or pulse pressure variation (PPV)—to more accurately predict volume responsiveness in the critically ill.²³ These techniques, however, are limited to patients receiving controlled ventilation and not breathing spontaneously. Another limitation may be that tidal volumes (Vt) of 8–10 cm³/kg are required to identify the cyclic variations in stroke volume indicative of fluid responsiveness. This would be problematic in ARDS patients who benefit from low Vt ventilation. Recently, however, PPV was found to accurately predict fluid responsiveness in ARDS patients ventilated with low Vt and high PEEP, albeit in a small study.²⁴ Further evaluation of these functional hemodynamic parameters in ALI/ARDS patients is needed. These tools may help the clinician judiciously provide volume expansion to only those who stand to increase their cardiac output without worsening pulmonary function.

NUTRITION

Patients with ARDS are characterized by a pro-inflammatory state and protein catabolism, which can lead to significant nutrition deficits. It is essential to meet the energy requirements of the lung-injured patient in order to minimize protein catabolism and maintain muscle strength. The goal of nutritional support for the lung-injured patient is to meet patients' caloric requirements and replete deficiencies of various nutrients while minimizing over- or underfeeding and their respective complications.²⁵ Enteral feeding is preferable to parenteral nutrition as it has a beneficial impact on gastrointestinal immune function and reducing infectious complications.²⁶

It is important to remember that many medications used in the treatment of ARDS may impact nutrition.

Corticosteroids impact glucose levels in the critically ill, which may result in hyperglycemia and the need for insulin. The use of propofol may result in extra calories secondary to the intralipid component of the drug.

In addition to meeting the patient's metabolic needs, certain nutrients may modulate the inflammatory response in lung-injured patients and have beneficial effects on pulmonary alveolar–capillary permeability, and hence lung and other organ function. The most promising dietary additives studied include fish oils rich in omega-3 polyunsaturated fatty acids (PUFA). A meta-analysis of three studies showed a decrease in mortality, increased ventilator-free days and reduced risk of organ dysfunction.²⁷ Other studies using enteral or parenteral omega-3 PUFAs failed to confirm the benefits from this meta-analysis.²⁸

PHARMACOTHERAPY

Evidence of safe and effective pharmacologic therapies for ARDS is limited. A variety of pharmacologic agents have been investigated including surfactant replacement, neuromuscular blocking agents, ketoconazole, nitric oxide, lisofylline, *N*-acetylcysteine, glucocorticoids, and β -agonist therapy. Few of these therapies have shown benefit and none have emerged as accepted treatments for lung injury.

Neuromuscular blocking agents are used in the management of ARDS to facilitate patient-ventilator synchrony in hopes of minimizing barotrauma, VILI, and excessive oxygen consumption. Three RCTs and a recent meta-analysis concluded that a continuous infusion of cisatracurium besylate for 48 hours after the diagnosis of ARDS reduced mortality. Cisatracurium did not decrease ventilator days or increase the risk of ICU-acquired weakness.²⁸ The mechanism by which cisatracurium decreases mortality is not entirely clear. Better ventilator synchrony may improve compliance and improve gas exchange or systemic inflammation may be decreased secondary to decreases in barotrauma and volutrauma. Another possibility is that during the early stages of ARDS a patient's inspiratory effort may add to the transpulmonary pressure created by the positive pressure ventilator breath, producing alveolar overdistention and lung injury. More research is needed to elucidate the exact mechanism by which mortality is improved.

Corticosteroids are the most studied drug in ARDS and significant controversy surrounds their use. Corticosteroids have a broad range of pharmacologic properties ranging from inhibition of transcription of inflammatory genes at low doses to inhibition of neutrophil degranulation at high doses.²⁹ Proponents of steroids assert they hasten the resolution of the fibro-proliferative stage of ARDS. There are many small studies that used variable steroid regimens differing in therapy timing, dosage, formulation, treatment duration, and tapering regimens. An ARDSNet study did not support the use of methylprednisolone therapy in ARDS and cautions that steroid therapy started more than 2 weeks after ARDS onset may increase mortality.³⁰ Conversely, a meta-analysis concluded that low-dose corticosteroids were associated with

improved mortality and morbidity outcomes in ARDS.²⁹ It is likely the effectiveness of corticosteroids in ARDS depends on the timing, dosage and underlying disease process and high-quality randomized controlled trials are needed to further characterize these variables.

After it was discovered that nitric oxide was a pulmonary vasodilator, it was rapidly adopted in the treatment of ARDS as a way to improve gas exchange and decrease the level of hypoxemia. Inhaled nitric oxide (INO) improves oxygenation in many ARDS patients, however, studies have not demonstrated any survival benefit in patients with ARDS. One meta-analysis of RCTs corroborated that INO does not reduce mortality in ARDS patients regardless of the severity of hypoxemia. Additionally, INO was associated with an increase in renal dysfunction.³¹ Given these findings it remains unclear what role INO should play (if any) in the treatment of ARDS. When all other evidence-based interventions (i.e., minimum PEEP, prone positioning, neuromuscular blockade) fail to produce adequate oxygenation, most would support a trial of an inhaled selective vasodilator (INO or inhaled prostacyclin) as salvage therapy.

MECHANICAL VENTILATION

Strategies of mechanical ventilatory support are central to the care of the ARDS patient. The overriding goals of MV are to maintain sufficient oxygenation ventilation and decrease the patient's work of breathing, all the while mitigating further VILI. This last goal is paramount to understanding why the strategy of lung-protective/low V_t ventilation improved mortality in the landmark ARDSNet study known as the Respiratory Management in ALI/ARDS trial (RMAT).³² Additionally, independent of the mode of delivering ventilatory support are the challenges of how to best target the optimal distending airway pressure as well as how to address the permissive hypercapnia that accompanies strategies of lung protection.

Understanding the importance of limiting alveolar stretch and barotrauma, the RMAT trial randomized 861 patients to either conventional V_t of 12 mL/kg or low V_t of 4–6 mL/kg of predicted ideal body weight. The low V_t group had their tidal volumes adjusted (between 4 and 6 mL/kg) to maintain plateau pressures ≤ 30 cm H₂O. The lower V_t strategy resulted in a 9% absolute mortality reduction (from 39.8% to 31.0%) and reduced ventilator-dependent days.³² The low V_t group also had lower plasma IL-6 levels, suggesting less lung inflammation that may have contributed to the lower rate of nonpulmonary organ dysfunction.

Both arms of this trial used the assist control (AC) mode of ventilation and a predetermined PEEP strategy based on the patient's required FiO_2 . The low V_t group required higher PEEP levels to maintain oxygenation, and some argue this contributed to the protection against cyclic alveolar opening and closing, a key component of VILI. The PEEP and FiO_2 strategy used by the ARDSNet investigators in RMAT remains unvalidated and is the source of continued controversy and investigation in lung injury. Studies supporting

higher versus lower PEEP strategies are conflicting.^{33–34} Likewise, while many clinicians have adopted the entire ARDSNet strategy from this landmark study, the AC mode of delivery has also not been proven to be the optimal ventilator mode.

An understanding of effect of transpulmonary versus transthoracic pressure as it relates to VILI is important. The end inspiratory alveolar pressure is estimated by the end inspiratory pause pressure reflecting the pressure that is required to distend the lung as well as the chest wall and abdominal contents at a static end inspiratory lung volume state. Therefore, in patients with chest wall edema, increased intra-abdominal pressure, or obesity, a higher plateau pressure is required with the same degree of lung elasticity when compared to a patient with normal body habitus, no edema and normal intra-abdominal pressure. From a clinical standpoint, this means that in these situations a higher plateau pressure may be allowed. Knowing precisely what that allowable pressure should be, however, is difficult in the absence of direct measurement of pleural pressure. Pressure measured at the distal esophagus is an estimate of the pleural pressure and has been used for partitioning the transpulmonary pressure from the transthoracic pressure.

Some level of PEEP is required to prevent low-volume lung injury and alveolar collapse during exhalation. Too much may lead to lung overinflation, barotrauma, and hemodynamic compromise. The challenge is to target the level of PEEP that keeps the patient breathing between the lower and upper inflection points of the pressure volume (P – V) curve (Figure 11-2). This is particularly difficult given the heterogeneous pattern of aeration and alveolar collapse in the ARDS patient so that different lung units have different P – V curves. Several techniques or guides to find the “best PEEP” exist including trending measures of pulmonary compliance along with oxygen delivery indices as one manipulates the PEEP,³⁵ using esophageal pressure measurements to estimate transpulmonary pressures to optimize PEEP,³⁶ CT lung morphology

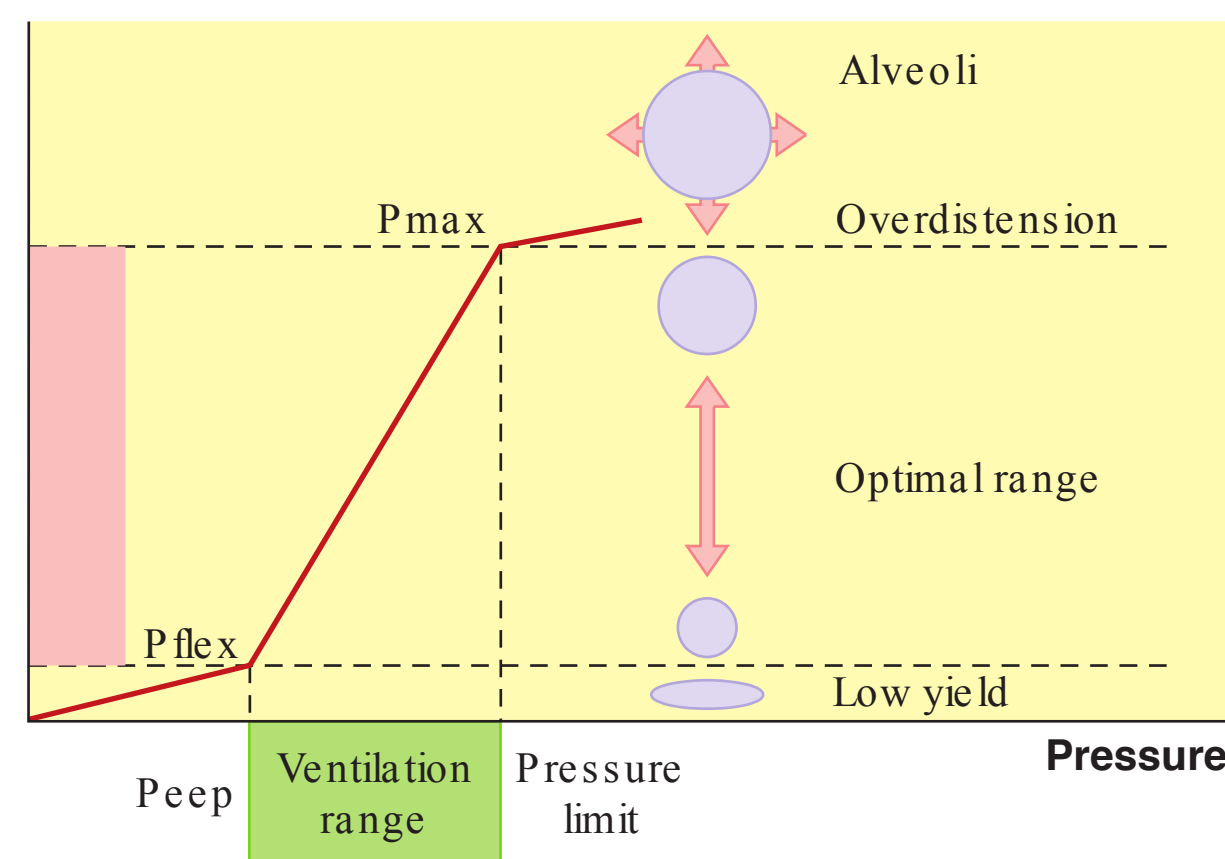


FIGURE 11-2 The lower and upper inflection points indicate the pressures at which lung recruitment begins and ends. The optimal pressure–volume relationship is between P_{flex} and P_{max} . The slope of the curve represents the potential for alveolar recruitment. (Used with permission from Patrick Neligan, MD.)

assessment to guide PEEP levels,³⁷ or using the continuous flow method to measure bedside P - V relationships.³⁸

Optimizing the PEEP during lung-protective ventilation is one challenge. Another important element is the hypercapnia resulting from a low V_t strategy. The discussed RMAT trial used increased respiratory rates and bicarbonate infusions to limit the hypercarbia and resultant acidosis. Both of these strategies are potentially problematic as high ventilatory rates may create auto-PEEP and overdistension, while bicarbonate infusions arguably increase the resultant CO_2 load and may worsen intracellular acidosis in the presence of tissue hypoperfusion. Interestingly, a growing body of literature supports that hypercapnia and moderate acidosis are not only well tolerated but may also be protective against lung and extrapulmonary organ dysfunction independent of the particular ventilator strategy. However, at this time, there are insufficient data to suggest that hypercapnia should be independently induced outside of the context of a protective ventilatory strategy.³⁹

In summary, current best ventilator practices in ARDS mechanical ventilation includes protective V_t of 6 mL/kg, maintaining plateau pressures ≤ 30 cm H_2O , and maintaining sufficient PEEP to prevent alveolar collapse.

ALTERNATIVE VENTILATORY STRATEGIES

In ARDS patients ventilated in the supine position, alveolar aeration is greater in the anterior/nondependent lung regions. Without PEEP, the ratio of ventilated nondependent to dependent lung zones approximates 2.5:1. At higher levels of PEEP, the distribution of ventilation becomes more homogenous but at the expense of overdistending and reducing the compliance of the nondependent (anterior) lung zones.⁴⁰ Prone ventilation results in a more homogenous inflation of the alveoli, which improves ventilation-perfusion matching. It also results in recruitment of dependent lung regions, optimized chest wall mechanics, reduction of right ventricular pressures in ARDS patients with cor pulmonale,⁴¹ and enhanced drainage of tracheobronchial secretions.⁴²

The prone position has been shown to consistently improve oxygenation in many retrospective and prospective studies.⁴³⁻⁴⁶ While several trials failed to demonstrate a survival benefit to prone positioning, a meta-analysis of these studies reported a mortality benefit. The PROSEVA trial was a recent multicenter RCT evaluating the effect of early prone position ventilation for greater than 16 hours a day in patients with severe ARDS. It demonstrated a reduction in 28-day and 90-day mortality.⁴⁷ The most recent surviving sepsis campaign guidelines suggest prone position ventilation in sepsis-induced ARDS patients with a $\text{PaO}_2/\text{FiO}_2 \leq 100$ mm Hg, in facilities experienced with proning patients.⁴⁸

Since ongoing VILI or atelectrauma results from cyclic opening and closing of lung units, ventilatory modes designed to keep the lung open more continuously have received considerable attention. Ventilator modes such as high-frequency oscillatory ventilation (HFOV) and airway pressure release

ventilation (APRV) are two modalities that achieve “open lung ventilation” via different mechanisms.

HFOV delivers very small tidal volumes at frequencies ranging from 3 to 15 Hz that limit alveolar distension, while maintaining a continuous distending pressure throughout inspiration and expiration, preventing alveolar collapse. Thus, HFOV proponents assert that this modality achieves the goals of a lung-protective strategy while improving continuous alveolar recruitment.⁴⁹ The OSCILLATE and OSCAR trials (both multicenter RCTs) evaluated the use of HFOV early in the treatment of ARDS. Neither trial demonstrated mortality benefit and the OSCILLATE trial was terminated early secondary to increased mortality in the HFOV group.^{50,51} HFOV should not be used as the primary initial ventilatory mode but could still be considered as salvage therapy.

Another modality that can be tailored to accomplish the goals of lung protection along with the benefit of continuous alveolar recruitment is APRV. APRV provides continuous positive airway pressure (CPAP) with very brief (typically < 1 second) releases of this pressure to augment CO_2 clearance. Maintaining CPAP above the alveolar closing pressure provides near-continuous alveolar recruitment. This improves oxygenation as well as ventilation via improved alveolar ventilation/passive gas exchange versus depending on tidal ventilation using conventional modes. Another advantage unique to APRV is maintenance of patients' spontaneous breathing. Allowing for spontaneous respiration improves the ventilation and perfusion distributions to a more physiologic pattern.³⁹ Maintenance of spontaneous breathing also improves the overall hemodynamic profile, cardiac performance, and blood flow to end organs. Last, patients spontaneously breathing on APRV have been consistently shown to have lower sedative and paralytic requirements.⁵³

But here again, the existing clinical trials have not demonstrated mortality reduction and the current successes are limited to physiologic endpoints. It should also be recognized that the driver for overinflation VILI is transalveolar pressure and spontaneous breathing with APRV adds the negative pleural pressure created with spontaneous breathing to the CPAP setting to establish the transpulmonary pressures affecting risk for VILI.

When optimal (lung protective) mechanical ventilation is failing and gas exchange derangements are life threatening, another option is extracorporeal lung support (ECLS) or extracorporeal membrane oxygenation (ECMO). While studies demonstrating definitive mortality benefit are lacking, a growing body of literature shows promise. The CESAR trial randomized ARDS patients to conventional treatment at non-ECMO facilities versus transport to an ECMO referral center where ultimately 75% of the treatment arm received venovenous ECMO early in their ARDS course.⁵⁴ This trial demonstrated a 6-month mortality benefit, which may be related to ECMO alone or the overall management strategy in the intervention group.

In summary, the relative success of any new ventilatory strategy depends on the control ventilatory strategy with which it is compared. Larger trials in the future should test these alternative ventilator strategies to the well-accepted ARDSNet protocol. Nevertheless, the improved physiologic

endpoints seen with these modalities, combined with sound understanding of physiology, make these alternatives viable and perhaps preferable to the conventional dogma of controlled ventilation in the supine position.

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Severe Asthma and COPD

Michael T. Dalley • Ari Ciment

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INTRODUCTION

Obstructive airway disease is the most common chronic pulmonary pathology encountered in emergency medicine. Its most common etiology, asthma, is characterized by bronchoconstriction and airway hyper-responsiveness to certain stimuli. These stimuli trigger inflammatory mediators that lead to airway inflammation, mucosal edema, and, ultimately, reversible bronchospasm.¹

Conversely, chronic obstructive pulmonary disease (COPD) is a disorder characterized by abnormal tests of expiratory flow demonstrating air flow obstruction that becomes fixed and does not change markedly over a period of months. It is a multifocal pathology encompassing the triad of emphysema, chronic bronchitis, and asthma.² The increasing prevalence and the large burden these disease entities impose on emergency medical care make the diagnosis and management of acute exacerbations vital to any health care provider.

EPIDEMIOLOGY

Approximately 25.9 million Americans had asthma in 2011, conferring an estimated financial burden of \$56 billion in annual health care costs.³ In the United States, there are approximately 2 million emergency department (ED) visits per year for acute asthma, with 14 million people reporting having had asthma “attacks” in the past year.⁴ Approximately

2% to 20% of all ICU admissions are attributed to severe asthma, with intubation and mechanical ventilation necessary in up to one third of ICU admissions,⁵ with mortality rates in patients receiving intubation ranging from 10% to 20%.⁶

COPD is the fourth most common cause of death in the United States, the third most common cause of hospitalization, and the only cause of death that is increasing in prevalence. The mortality of all patients while hospitalized for a COPD exacerbation is approximately 5% to 14%,⁷ while mortality of COPD patients admitted to an ICU for an exacerbation is 24%. For patients 65 years or older and discharged from the ICU after treatment of a COPD exacerbation, the 1-year mortality is 59%.⁷

PATHOPHYSIOLOGY

Asthma

The Global Initiative for Asthma defines asthma as a heterogeneous disease characterized by chronic airway inflammation. It is defined “by the history of respiratory symptoms such as wheeze, shortness of breath, chest tightness and cough that vary over time and in intensity, together with variable expiratory airflow limitation.” The variable airflow obstruction within the lung is often reversible, either spontaneously or with treatment. Exacerbations refer to the recurrent symptomatic flare-ups associated with this chronic disorder.⁸

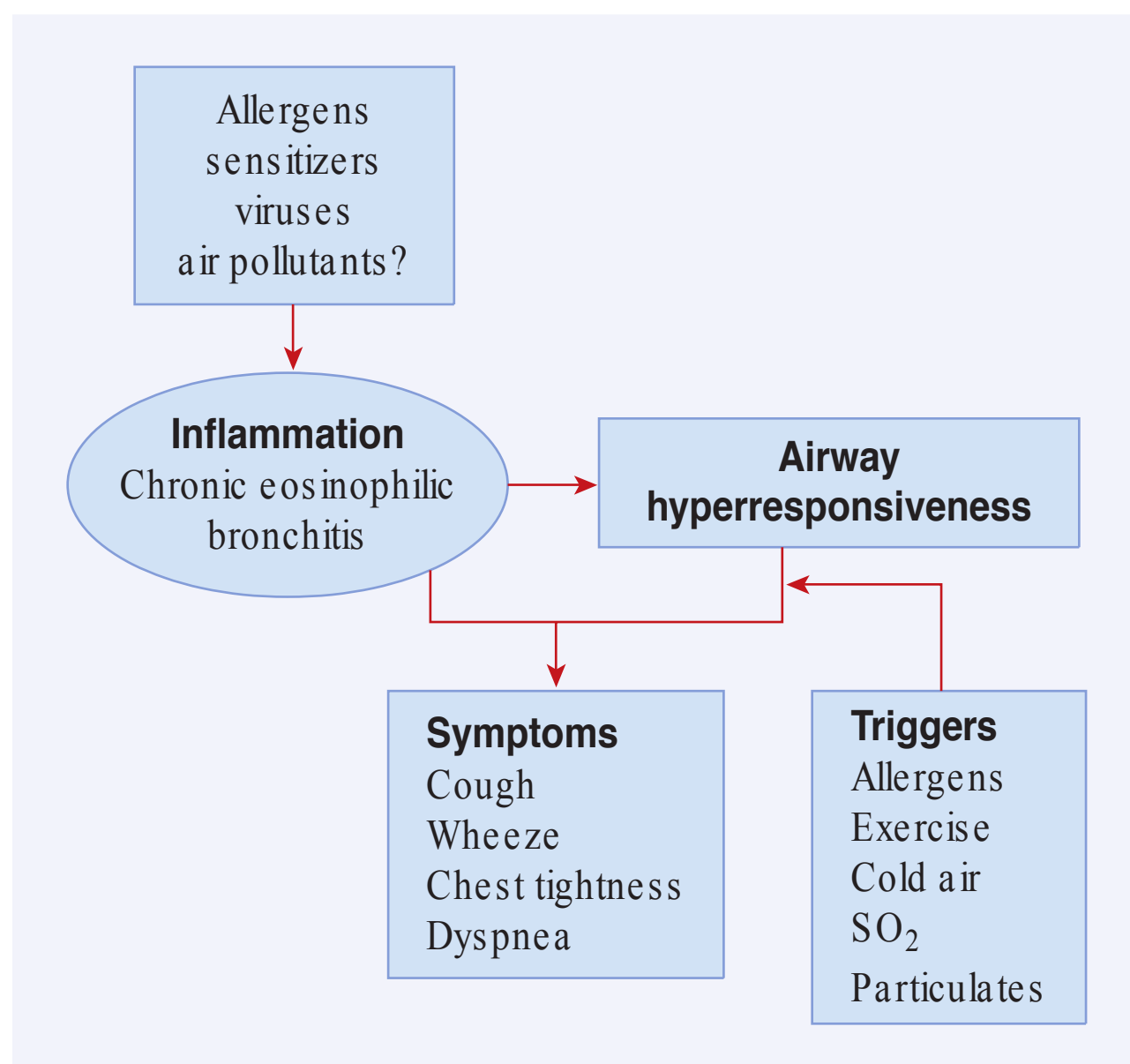


FIGURE 12-1 Inflammation in the airways of asthmatic patients leading to airway hyperresponsiveness and symptoms. (Reproduced with permission from Fauci AS, Kasper DL, Braunwald E, et al: *Harrison's Principles of Internal Medicine*, 17th edition. New York: McGraw-Hill Inc; 2008.)

Asthma is characterized by airway inflammation with an abnormal accumulation of inflammatory mediators in response to various stimuli. Acutely, this accumulation leads to a reversible reduction of airway diameter caused by smooth muscle contraction, vascular congestion, bronchial wall edema, and thickened secretions.

Chronic asthma can lead to airway remodeling, with sub-epithelial collagen deposition and increased airway resistance that manifests as a progressive decline in forced expiratory volume in 1 second (FEV1) measurements. After airway remodeling has occurred, the pathologic changes may become irreversible.

Pathologic findings in patients with chronic asthma include bronchial wall thickening due to inflammation and edema, bronchial narrowing or obstruction, and the presence of mucus plugs that at times may be large and thick. This obstruction leads to alveolar hyperinflation and, in a subset of patients, may lead to the formation of bullae, the potential for bullae rupture, and the development of pneumothoraces (Figures 12-1 and 12-2).

COPD

The Global Initiative for Chronic Obstructive Lung Disease (GOLD)—a project initiated by the National Heart, Lung, and Blood Institute (NHLBI) and the World Health Organization (WHO) defines COPD as follows: “Chronic obstructive pulmonary disease (COPD), a common preventable and treatable disease, is characterized by airflow limitation that is usually progressive and associated with an enhanced chronic inflammatory response in the airways and the lung to noxious

particles or gases. Exacerbations and comorbidities contribute to the overall severity in individual patients.”⁹

COPD classically involves two distinct and often overlapping phenotypes: Chronic bronchitis is defined by excessive mucus production resulting in airway obstruction and hyperplasia of mucus-producing glands. Damage to the endothelium impairs mucociliary function that inhibits the clearance of bacteria and mucous. Inflammation and secretions, worsened due to the decreased mucus clearance, provide the obstructive component of this disease. Emphysematous changes may be present to a variable degree. This leads to increased cardiac output in an attempt to compensate for decreased ventilation. The resulting rapid circulation through a poorly ventilated lung represents a V/Q mismatch with consequent hypoxemia and polycythemia, which may ultimately lead to cor pulmonale and right heart failure. Concomitant hypercapnia and respiratory acidosis round out the classic “Blue Bloater” appearance in such a later stage chronic bronchitic patient.

Emphysema, the second phenotype, is defined by destruction of airways distal to the terminal bronchiole. Pathologically, this disease involves the gradual destruction of alveolar septae and of the pulmonary capillary bed, leading to decreased ability to oxygenate blood. The body compensates with hyperventilation and the lowering of cardiac output. This V/Q mismatch results in relatively limited blood flow through a fairly well-oxygenated lung (as opposed to chronic bronchitis, in which there is rapid circulation through a poorly ventilated lung). The low cardiac output ultimately leads to systemic tissue hypoxia and pulmonary cachexia. Eventually, these patients develop muscle wasting and weight loss and have classically been referred to as “pink puffers.”

The diagnosis, severity, clinical course, and response to treatment of all obstructive lung diseases (OLDs) can best be evaluated objectively by testing pulmonary function. OLD causes a delay in emptying lung volume. Normally, an individual can forcefully expel all of the air in the lungs (the vital capacity) within 4–6 seconds. In established OLD, patients may continue to expire during a forced expiratory maneuver for 10–20 seconds or more.

While all individuals have flow limitation during a forced expiration, those with obstructive airway disease demonstrate flow limitation with less effort and at lower airflow. The three lung abnormalities that reduce flow during forced expiration are decreased lung recoil pressure, increased resistance of the airways, and increased tendency of airways to collapse. Decreased lung recoil pressure causes a lower distending pressure between the airway and the surrounding pleural pressure, promoting a tendency for the airways to narrow. Increased resistance of the airways, especially in the periphery of the lung, creates increased pressure drops along the airways during expiration, thus promoting the tendency of the airways to constrict before the entire tidal volume is expelled. Bronchial smooth muscle constriction, inflammatory products encroaching upon the airway lumen, and decreased tethering of the airway by the alveolar septa also cause airways to collapse more easily.¹⁰

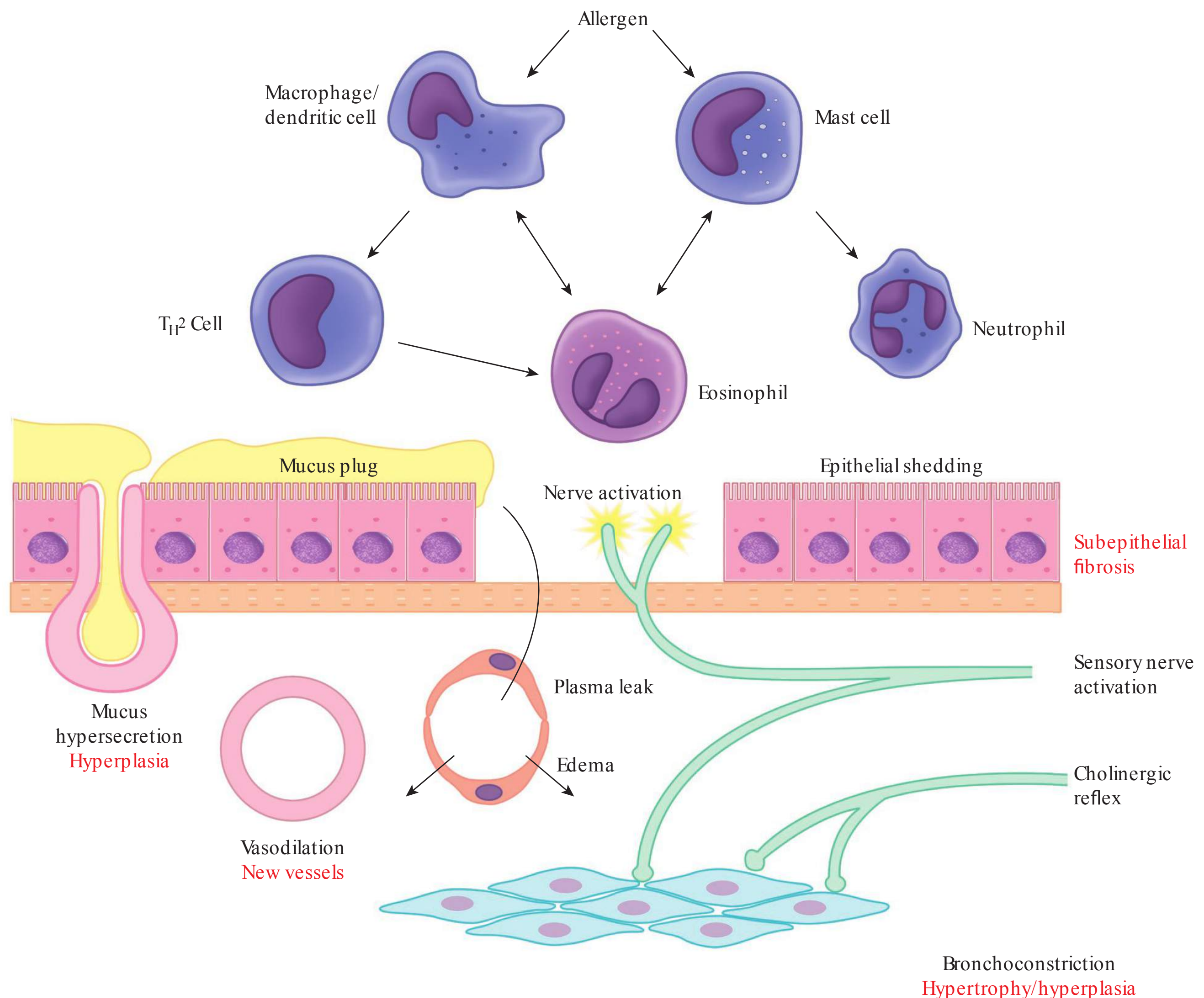


FIGURE 12-2 Pathophysiology of asthma showing participation of several interacting inflammatory cells and resulting in acute and chronic inflammatory effects on the airway. (Reproduced with permission from Fauci AS, Kasper DL, Braunwald E, et al: *Harrison's Principles of Internal Medicine*, 17th edition. New York: McGraw-Hill Inc; 2008.)

The airflow limitation in emphysema can be attributed to the decreased elastic recoil of the lung, in chronic bronchitis to the increased peripheral airway resistance, and in asthma to the increased tendency of airways to collapse.¹⁰

CLINICAL PRESENTATION

Asthma classically presents with a triad of symptoms that include cough, wheeze, and shortness of breath. However, certain patients may present with only one or two of these symptoms. Patients may complain of chest tightness or band-like constriction across the chest. The cough may be dry or productive with pale yellow sputum. Wheezing may be subjective in patients familiar with the term and used to describe a variety of sounds including upper airway noises from the throat or nares. Since many of these complaints are

consistent with many pulmonary pathologies, it can be hard to diagnose asthma based on chief complaint alone. However, certain historical clues such as episodic symptoms, characteristic triggers, and personal or family history of atopy or asthma as a child raise the likelihood.

There are four major causes of acute decompensation in COPD patients: (1) superimposed respiratory illness, (2) noxious environmental exposure, (3) noncompliance with medications, and (4) continued cigarette smoking. Patients complain of dyspnea, cough, and increased sputum production. During acute exacerbations, patients may also present with wheezing, particularly with exertion. As the disease becomes more chronic, intervals between acute exacerbations lessen. Patients may also complain of morning headaches, which are attributed to increased hypercapnia while asleep, leading to worsening respiratory acidosis.

FIGURE 12-3 Risk factors for death from asthma. (Reproduced with permission from the US Department of Health and Human Services, National Institute of Health, National Heart, Lung, and Blood Institute. *Expert Panel Report 3: Guidelines for the Diagnosis and Management of Asthma.*)

Asthma history

Previous severe exacerbation (e.g., intubation or ICU admission for asthma)
Two or more hospitalizations for asthma in the past year
Three or more ED visits for asthma in the past year
Hospitalization or ED visit for asthma in the past month
Using >2 canisters of SABA per month
Difficulty perceiving asthma symptoms or severity of exacerbations
Other risk factors: lack of a written asthma action plan, sensitivity to *Alternaria*

Social history

Low socioeconomic status or inner-city residence
Illicit drug use
Major psychosocial problems

Comorbidities

Cardiovascular disease
Other chronic lung disease
Chronic psychiatric disease

Key: ED, emergency department; ICU, intensive care unit; SABA, short-acting beta₂-agonist

Sources: Abramson et al. 2001; Greenberger et al. 1993; Hardie et al. 2002; Kallenbach et al. 1993; Kikuchi et al. 1994; O'Hollaren et al. 1991; Rodrigo and Rodrigo 1993; Strunk and Mrazek 1986; Suissa et al. 1994

HISTORY AND PHYSICAL EXAMINATION

The spectrum of disease that presents to the emergency department is vast, and the severity of exacerbation can progress in minutes. Caregivers should be familiar with the risk factors for death from asthma (Figure 12-3),¹¹ and if there is only time for an abbreviated history, it should be focused on the predictors of fatal outcomes. The American Thoracic Society (ATS) workshop on refractory asthma defines severe asthma based on two major criteria: (1) Daily use of high-dose inhaled corticosteroids and/or (2) use of systemic corticosteroids; and 7 minor criteria (symptoms; frequency, severe or life threatening exacerbations; lung function; controller use; and loss of control when corticosteroids were tapered. At least one major and two minor criteria imply the working definition of severe asthma.¹²

On physical examination, widespread, high-pitched, musical wheezes are characteristic of asthma; however, these findings are nonspecific and may be absent in severe obstruction. The most concerning physical findings suggestive of air flow obstruction include conversational dyspnea or inability to speak at all, tachypnea (RR > 30), tachycardia (HR > 130), and a prolonged expiratory phase of respiration (decreased I:E ratio). More ominous signs include tripod positioning, retractions, and pulsus paradoxus (a fall in systolic blood pressure greater than 12 mm Hg during inspiration).

Signs indicating impending respiratory failure include a silent chest (no wheezing is worse than wheezing), inability to recline or lay supine in the stretcher, altered mental status, and paradoxical respirations (Figure 12-4).

ASSESSMENT OF LUNG FUNCTION

Pulmonary function tests are critical tools in the diagnosis and management of OLD exacerbations. Measurement of peak expiratory flow rate (PEFR) and spirometry are the tests most often used in the diagnosis of asthma or an exacerbation and the best objective evaluation for risk stratifying patients, monitoring response to therapy, and determining final disposition in exacerbations of OLD.

The PEFR, or “peak flow,” is measured during a brief, forceful exhalation. The resulting measurements are highly dependent on the patient’s expiratory effort and technique. It is preferable to have a known established baseline measure, obtained when the patient is feeling well, with which to compare subsequent readings. However, many if not most of the asthmatics seen in the ED have not used a peak flow meter before, in which case you can predict the normal PEFR utilizing their height and age. For instance, a 40-year-old man who is six feet and 3 inches tall should have a peak expiratory flow of around 659 L/minute with 80–100% of that value considered the normal range.¹³

Serial measurements performed at presentation and 30–60 minutes after initial treatment are recommended.¹⁹ However, in patients experiencing a severe or life-threatening exacerbation with impending respiratory failure, PEFR testing is not warranted and should not preclude immediate therapy.

Spirometry, which includes measurement of FEV1 and forced vital capacity (FVC), provides additional objective information in the diagnosis and management of OLD. Variable/reversible airflow obstruction is the hallmark of asthma. Progressively worsening fixed airflow obstruction is the hallmark of COPD. Since bronchospasm is not the major

	Mild	Moderate	Severe	Subset: Respiratory arrest imminent
Symptoms				
Breathlessness	While walking Can lie down	While at rest (infant—softer, shorter cry, difficulty feeding) Prefers sitting	While at rest (infant—stops feeding) Sits upright	
Talks in	Sentences	Phrases	Words	
Alertness	May be agitated	Usually agitated	Usually agitated	Drowsy or confused
Signs				
Respiratory rate	Increased	Increased Guide to rates of breathing in awake children: <i>Age</i> <2 months 2–12 months 1–5 years 6–8 years	Often >30/minute <i>Normal rate</i> <60/minute <50/minute <40/minute <30/minute	
Use of accessory muscles; suprasternal retractions	Usually not	Commonly	Usually	Paradoxical thoracoabdominal movement
Wheeze	Moderate, often only end expiratory	Loud; throughout exhalation	Usually loud; throughout inhalation and exhalation	Absence of wheeze
Pulse/minute	<100	100–120 Guide to normal pulse rates in children: <i>Age</i> 2–12 months 1–2 years 2–8 years	>120 <i>Normal rate</i> <160/minute <120/minute <110/minute	Bradycardia
Pulsus paradoxus	Absent <10 mmHg	May be present 10–25 mmHg	Often present >25 mmHg (adult) 20–40 mmHg (child)	Absence suggests respiratory muscle fatigue
Functional Assessment				
PEF percent predicted or percent personal best	≥70 percent	Approx. 40–69 percent or response lasts <2 hours	<40 percent	<25 percent Note: PEF testing may not be needed in very severe attacks
PaO ₂ (on air)	Normal (test not usually necessary)	≥60 mmHg (test not usually necessary)	<60 mmHg: possible cyanosis	
and/or PCO ₂	<42 mmHg (test not usually necessary)	<42 mmHg (test not usually necessary)	<42 mmHg: possible respiratory failure (See pages 393–394, 399.)	
SaO ₂ percent (on air) at sea level	>95 percent (test not usually necessary) Hypercapnia (hypoventilation) develops more readily in young children than in adults and adolescents.	90–95 percent (test not usually necessary)	<90 percent	
<p>Key: PaO₂, arterial oxygen pressure; PCO₂, partial pressure of carbon dioxide; PEF, peak expiratory flow; SaO₂, oxygen saturation</p> <p>Notes:</p> <ul style="list-style-type: none"> ■ The presence of several parameters, but not necessarily all, indicates the general classification of the exacerbation. ■ Many of these parameters have not been systematically studied, especially as they correlate with each other. Thus, they serve only as general guides (Cham et al. 2002; Chey et al. 1999; Gorelick et al. 2004b; Karras et al. 2000; Kelly et al. 2002b and 2004; Keogh et al. 2001; McCarren et al. 2000; Rodrigo and Rodrigo 1998b; Rodrigo et al. 2004; Smith et al. 2002). ■ The emotional impact of asthma symptoms on the patient and family is variable but must be recognized and addressed and can affect approaches to treatment and followup (Ritz et al. 2000; Strunk and Mrazek 1986; von Leupoldt and Dahme 2005). 				

FIGURE 12-4 Formal evaluation of asthma exacerbation severity in the urgent or emergency care setting. (Reproduced with permission from the US Department of Health and Human Services, National Institute of Health, National Heart, Lung, and Blood Institute. *Expert Panel Report 3: Guidelines for the Diagnosis and Management of Asthma.*)

pathologic mechanism behind COPD, the improvement in pulmonary function measurement during therapy is less than that of asthmatics.

Indicators for admission to the hospital include PEFR less than 100 mL/min or FEV1 less than 1 L prior to treatment, PEFR or FEV1 less than 40% baseline/predicted, failure of PEFR to increase greater than 10% following initial treatment, and PEFR that does not reach 80% of predicted following aggressive therapy.¹¹

Pulse oximetry measurement is desirable in all patients with acute exacerbations of OLD to exclude hypoxemia. However, an isolated pulse oximetry reading at triage is not predictive in most cases, and serial monitoring can provide more subtle evidence for or against the need for hospital admission.

LABORATORY STUDIES

Routine laboratory studies are not contributory in the evaluation of exacerbations of OLD, but are used to diagnose or exclude other conditions, detect or confirm impending respiratory failure and theophylline toxicity, and diagnose comorbid conditions that might compromise therapy.

Arterial blood gas (ABG) measurement provides important information in severe asthma exacerbations. The test may reveal dangerous levels of hypercapnia secondary to poor ventilation due to exhaustion. ABGs are indicated in patients with fatigue or exhaustion, suspected hypoventilation, SaO₂ 90%, or PEFR 25% predicted after aggressive therapy. In severe asthmatics, even a normal pH or Pco₂ should prompt consideration of intubation, since normalization of these values may indicate tiring of the respiratory muscles. In COPD patients, ABG values are helpful in determining whether inadequacy of ventilation (hypercapnia) is an acute decompensation or a chronic compensation.

Chest radiographs in exacerbations of obstructive disease are usually nondiagnostic, but are indicated to rule out secondary causes of wheezing (i.e., congestive heart failure, pneumothorax, pneumomediastinum, pneumonia, etc.).

TREATMENT

The goals of therapy for acute exacerbations of OLD remain constant throughout the spectrum of the disease process: improving hypoxemia, reversal of acute bronchospasm, and prevention of post-therapy relapse. The primary treatment consists of the administration of oxygen, inhaled β_2 -agonists, and systemic corticosteroids; these should be given to all patients with acute exacerbations requiring medical evaluation. The severity of the asthma exacerbation determines the intensity of treatment and the frequency of patient monitoring (Figure 12-5).¹¹

Inhaled β_2 -Adrenergic Agonist

Short acting Inhaled β_2 agonists are sympathomimetic agents which stimulate β_2 receptors in airway cells to produce

a variety of effects. Chief among these are smooth muscle relaxation and bronchodilation caused by activation of adenylyl cyclase to produce cyclic 3'5' adenosine monophosphate (AMP). Inhaled β_2 -agonists should be administered immediately on presentation. β_2 agonists can be given via nebulization or metered dose inhaler (MDI), but most guidelines recommend the use of nebulization for severe asthma.^{14,15} Albuterol is usually given as 2.5–5 mg by intermittent nebulization every 20 minutes for three doses, then 2.5 to 10 mg every one to four hours as needed or via continuous nebulization at 10–15 mg/hr. The current literature has yet to prove superiority of either dosing method.

A meta-analysis of results from 6 randomized trials indicated that intermittent and continuous administration have similar effects on both lung function and the overall rate of hospitalizations.¹⁶ However, a Cochrane review of eight trials suggests that continuous nebulization resulted in greater improvement in peak flow and a reduction in hospital admissions among patients with severe asthma.¹⁷ In mild to moderate asthma exacerbations, albuterol MDI with spacer can be used in the following way: 4 puffs every 10 minutes, or 8 puffs every 20 minutes, for up to 4 hours. They can be continued thereafter every one to four hours as needed.^{14,15}

Anticholinergic Agents

Ipratropium bromide competitively inhibits muscarinic cholinergic receptors to produce bronchodilation. Inhaled ipratropium bromide has a relatively slow onset of action as compared to β_2 adrenergic agonists and is not recommended as monotherapy in the emergency department. However therapy with inhaled ipratropium bromide is typically used in conjunction with β_2 adrenergic agonists. It works synergistically with β_2 -agonists and has been shown to reduce hospitalizations in patients with severe airflow obstruction.¹⁸ It reduces bronchoconstriction in the central airways, what may explain the better therapeutic outcomes when treating COPD—as opposed to asthma—exacerbations. The adult dosing of ipratropium for nebulization is 500 mcg every 20 minutes for three doses, then as needed. If an MDI is used, 8 inhalations every 20 minutes, then as needed for up to three hours is recommended. It is worth noting that the National Asthma Education and Prevention Program Expert Panel report 3 (NAEPP-EPR3) guidelines also lists ipratropium bromide as only a helpful adjunctive therapy in the ED, and there is no apparent benefit of continuing ipratropium during hospitalization.

Newer anticholinergic agents may play a major role in the prevention of severe asthma/COPD exacerbations. Tiotropium bromide, the once-daily, long-acting anticholinergic, is not mentioned in the last NAEPP-EPR3 partly because it has only recently been added as an effective tool in asthma control and has not been yet shown effective for an acute exacerbation.¹⁹ Of the three major muscarinic receptors, M1 and M3 are responsible for vasoconstriction and M2 with vasodilation. Since tiotropium bromide selectively inhibits

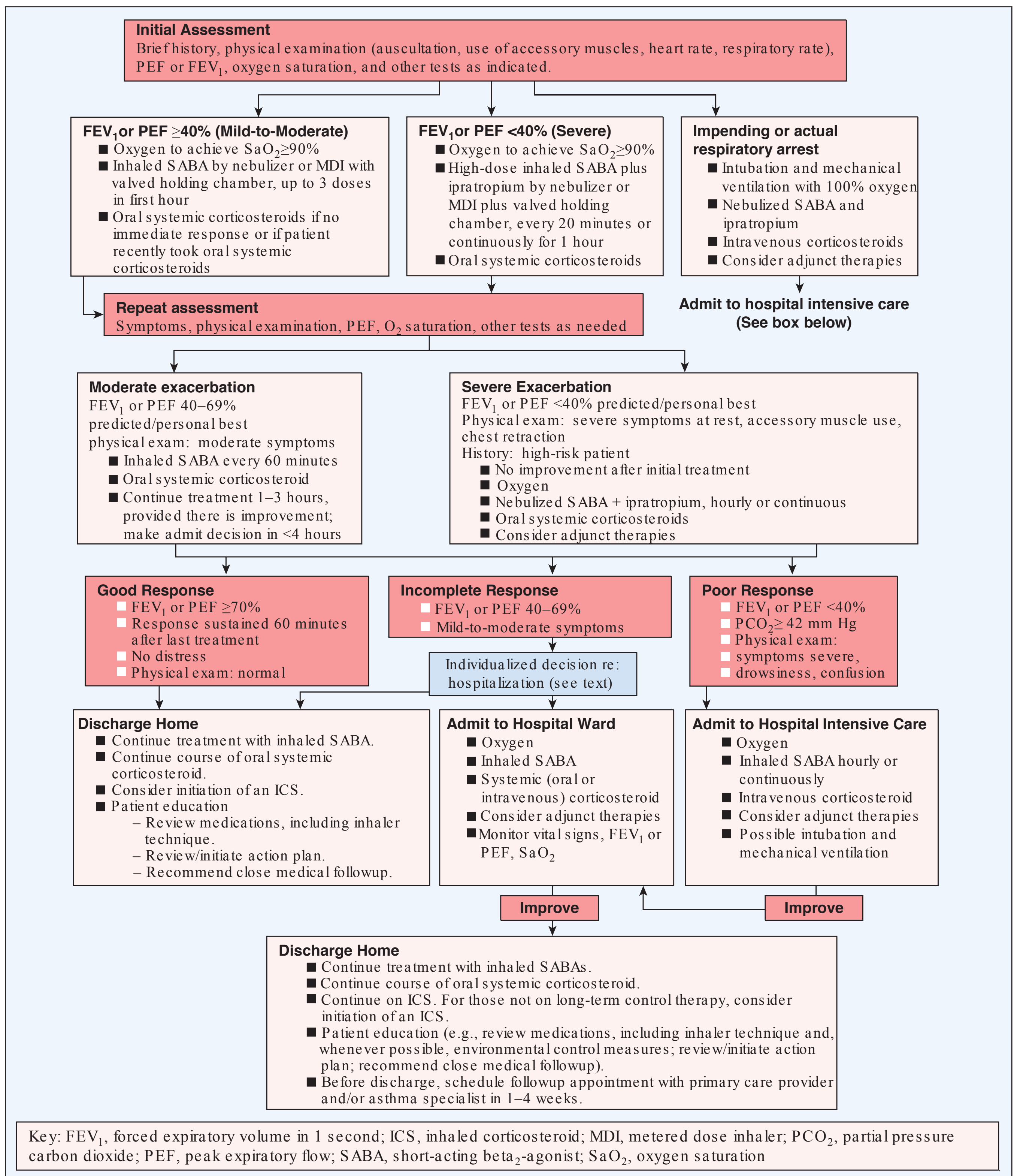


FIGURE 12-5 Management of asthma exacerbations: emergency department and hospital-based care. (Reproduced with permission from the US Department of Health and Human Services, National Institute of Health, National Heart, Lung, and Blood Institute. *Expert Panel Report 3: Guidelines for the Diagnosis and Management of Asthma*.)

M1 and M3, there is a theoretical advantage of having less “paradoxical bronchospasm” than when using ipratropium bromide, which blocks all 3 receptors.

Systemic Steroids

Systemic steroids should be administered to all patients presenting with severe OLD exacerbations. Meta-analyses have shown that use of systemic corticosteroids is associated with more rapid improvement in lung function, fewer hospitalizations, and a lower rate of emergency department recidivism after discharge^{20,21} In patients with normal mental status and without conditions that would affect GI absorption, oral administration is preferred over intravenous, since no studies have proved superiority in the rate of improvement of lung function or length of stay.²² The most recent guidelines from the National Asthma Education and Prevention Program Expert Panel report 3 (NAEPP-EPR3) recommends the use of 40 to 80 mg per day in one or two divided doses.¹¹

IMPENDING RESPIRATORY FAILURE

Intensive therapy with inhaled bronchodilators and systemic corticosteroids is usually sufficient to reduce airflow obstruction and alleviate symptoms in patients with exacerbations of OLD. However, a small percentage of patients will show signs of worsening ventilation. It is recommended that intubation not be delayed after it has been deemed necessary,¹⁸ and it is this subset of patients on which the rest of the chapter will focus.

Intubation and mechanical ventilation in OLD are complex and fraught with potential complications. Therefore, prevention of intubation is an important goal in the treatment of severe, acute OLD. Various second-line therapies have been suggested and bear consideration for critically ill patients who would otherwise require intubation.

Intravenous magnesium sulfate can be considered in patients with life-threatening exacerbations and in those whose exacerbations remain severe after 1 hour of intensive conventional treatment.^{23,24} Magnesium sulfate is thought to inhibit bronchial smooth muscle contraction by inhibiting intracellular influx of calcium. The dose is usually 2 g over 20 minutes in adults and 25–75 mg/kg in children (up to a maximum of 2 g), and its selective use is common.²⁵

Heliox is a mixture of oxygen and helium that decreases airway resistance by reducing airflow turbulence in the lungs, thus reducing the work of breathing. It is available in a variety of percentages. An 80:20 mix (80% helium, 20% oxygen) contains about the same amount of oxygen as room air, but mixes with higher percentages of oxygen are available. The higher the helium content, the less viscous the mixture, thus the greater the tendency toward laminar flow and a lower work of breathing. However, the higher the helium content, the lower the oxygen content, and the greater the tendency toward hypoxia. For patients with severe exacerbations of their disease, the NAEPP-EPR3 calls this form of therapy promising but gives it a conditional recommendation, citing the need for a large multicenter study.¹⁸

NONINVASIVE VENTILATION

Noninvasive positive pressure ventilation (NPPV) refers to positive pressure ventilation delivered through a noninvasive interface such as a facemask rather than the more invasive endotracheal tube. Typically, NPPV refers to continuous positive airway pressure (CPAP) and bilevel positive airway pressure (BPAP).

CPAP delivers positive airway pressure at a constant level throughout the respiratory cycle, effectively splinting the upper airway open and preventing upper airway collapse. BPAP delivers both inspiratory positive airway pressure (IPAP) and expiratory positive airway pressure (EPAP). Although we do typically call BPAP by the terms “BiPAP” or “BIPAP,” those terms are actually names of ventilators that deliver BPAP.

In OLD, some gas remains trapped in alveoli at end expiration, causing levels of positive end-expiratory pressure (PEEP) above those seen in normal physiology. Since this PEEP comes from within the lung itself, it is termed “auto-PEEP.” It may seem counterintuitive to then apply additional external PEEP, but studies have shown that a low level of applied CPAP may offset the deleterious effects of auto-PEEP.²⁶ The proposed mechanism in externally applied PEEP both delays or prevents airway collapse (reducing or relieving airway obstruction) and lessens the work of breathing (allowing extra time for other modalities to exert their effect). The addition of inspiratory pressure support to CPAP (aka “BiPAP”) improves tidal volume in proportion to the amount of pressure applied.

NPPV has prevented intubations in a variety of respiratory conditions in addition to OLD exacerbations. Randomized control trials have demonstrated that NPPV decreases respiratory rate, dyspnea, $Paco_2$, length of stay, and rates of intubation and improves mortality in COPD exacerbations.²⁷ Pathophysiologically, acute asthma exacerbations are similar in mechanism but there is less literature supporting NPPV in the treatment of asthma exacerbations.²⁸ In a recent small random controlled trial of 53 patients, for instance, ICU and hospital stay were significantly shorter in the NPPV group and the mean dose of inhaled bronchodilator was significantly less.²⁹ The most recent Cochrane database reviewing the use of NPPV in severe asthma identified only six trials for inclusion. Given the paucity of data supporting the use of NPPV in such patients, the authors encouraged larger, prospective randomized controlled trials to study this population.³⁰

According to the NAEPP-EPR3, a trial of NPPV before intubation and mechanical ventilation should be considered in select patients with acute asthma exacerbation and respiratory failure, provided they are alert and can tolerate and cooperate with the therapy.²⁸ Initial settings call for an initial expiratory pressure of 3 cm H_2O increased every 15 minutes to a maximum of 5, and an initial inspiratory pressure of 8 cm H_2O increased every 15 minutes to a maximum pressure of 15 or until the respiratory rate is less than 25 breaths/min.³¹ Nebulizer therapy should be continued throughout the administration of NPPV. Many facilities use a dedicated NPPV machine, although some practitioners prefer

to administer NPPV using a traditional ventilator; with this method, if the patient fails NPPV therapy and requires intubation, the ventilator is already in place.

INTUBATION AND MECHANICAL VENTILATION IN RESPIRATORY FAILURE

Criteria for Intubation

In spite of all efforts for prevention of intubation, patients may still decompensate and require intubation and mechanical ventilation. Clinically, there are four major indications for intubation: (1) cardiac arrest, (2) respiratory arrest or profound bradypnea, (3) physical exhaustion, and (4) altered mental status such as lethargy or agitation. Patients may tell you, “I am too tired to breathe,” or “I can’t go on any more”; these statements alone are ominous and should trigger consideration for intubation.

Objectively, an ABG may be helpful and indicate failed non-invasive therapy and the need for intubation. An ABG showing progressive hypoxemia, hypercapnia, and respiratory acidosis in a patient who has changes in mental status should immediately trigger airway intervention.³⁰ Even a normal pH or P_{CO_2} should prompt consideration of intubation, since normalization of these values may indicate tiring of the respiratory muscles.

Intubation Technique

Intubation with a rapid sequence of sedation followed by muscle paralysis is the preferred method for airway control in the emergency department setting.³³ Airway control should be obtained by an experienced care provider because even minor manipulation of the airway during an acute OLD exacerbation can lead to laryngospasm and worsen bronchospasm.

Of the available sedatives used during rapid sequence intubation (RSI), ketamine and propofol offer the best therapeutic advantages during an OLD exacerbation. Ketamine stimulates the release of catecholamines and may have a direct relaxation effect on bronchial smooth muscle, leading to bronchodilation.³⁴ Side effects include hypersecretion, hypertension, arrhythmias, and hallucinations, although pretreatment with atropine may reduce or eliminate some of these. It is contraindicated in patients with ischemic heart disease, hypertension, preeclampsia, and increased intracranial pressure.

Propofol is a short-acting sedative with bronchodilatory effects. It has rapid onset of action and is very short acting, which allows for rapid awakening. It is an excellent alternative for patients with elevated blood pressure during the peri-intubation period. Some practitioners also prefer propofol because it can be easily used for ongoing sedation.

Setting the Ventilator

The physiology of patients with OLD exacerbations presents a unique, complex challenge when these patients are placed



TABLE 12-1: Initial Ventilator Settings for the Intubated Asthmatic Patient

Controlled mechanical ventilation at 10 breaths/min
Tidal volume at 7–8 mL/kg (ideal body weight)
Peak inspiratory flow at 60 L/min (constant flow) or 80–90 L/min (decelerating flow)
Fraction of inspired oxygen at 1.0

Reproduced with permission from Brenner B, Corbridge T, Kazzi A: Intubation and mechanical ventilation of the asthmatic patient in respiratory failure, *JEmerg Med*. 2009 Aug;37(2 Suppl):S23–S34.

on mechanical ventilation. Airway obstruction in the OLD exacerbation is characterized by normal inhalation followed by an impaired subsequent exhalation phase. This typically leads to some level of lung hyperinflation (auto-PEEP), which in severe cases may ultimately lead to hypotension and/or barotrauma.³⁵ Ventilatory strategies are adopted to reduce such hyperinflation. More elaborate detail on the specifics regarding mechanical ventilation in the OLD patient may be found in the mechanical ventilation section of this textbook, but some key points are summarized below:

Three elements that make up a sound ventilator strategy to reduce hyperinflation and auto-PEEP in the intubated asthmatic patient (Table 12-1) include: (1) reducing the respiratory rate, (2) increasing the inspiratory flow rate and (3) reducing the tidal volume. The first 2 steps essentially aim to increase the I:E ratio to ensure adequate lung emptying. Although the aforementioned steps may lead to hypercapnia, this so-called “permissive hypercapnia” is usually well tolerated. Anoxic brain injury and severe myocardial dysfunction are some relative contraindications to permissive hypercapnia because of the potential hypercapnia-induced dilation of cerebral blood vessels and decreased myocardial contractility.³⁶ Auto-PEEP and plateau pressure (Pplat) are measured pressures used as surrogate markers of lung inflation. These measurements typically depend on patient–ventilator synchrony and absence of patient effort, although paralysis is generally not required. Neither parameter has been validated as a predictor of complications due to mechanical ventilation, but experts agree that complications are rare when Pplat is less than 30 cm H₂O and auto-PEEP is less than 15 cm H₂O.³⁷

Medical Management

As with all intubated patients, effective sedation is paramount. A good sedative strategy should allow synchrony between the patient and the ventilator, thus preventing auto-PEEP. It should also prevent dangerous self-extubation. Propofol is preferred by many because it may possess some bronchodilatory properties and is easy to titrate.³⁷ Morphine use should be avoided because it can cause histamine release, bronchospasm, vomiting, and drying of secretions.³⁷ Ketamine is typically used more often during intubation (discussed earlier)

but is occasionally used in the intubated refractory status asthmaticus ICU patient.³⁸

Inhaled anesthetic agents such as sevoflurane and isoflurane are occasionally employed as well in refractory cases but there are no random controlled trials on such therapies.³⁹ Neuromuscular blockade (NMB) during mechanical ventilation may reduce the risk of barotrauma, avoid coughing and dyssynchronous breathing, and allow the respiratory muscles to rest. However, prolonged use can cause myopathy, particularly when used in conjunction with corticosteroids. NMBs are generally only recommended in patients in whom deep sedation alone does not allow synchrony with the ventilator.

Systemic corticosteroids and inhaled β -agonists are the mainstay of asthma therapy prior to intubation, and are continued while on mechanical ventilation. High flow aerosolized (HFA, aka multidose inhaler [MDI]) or nebulizer treatments should be added to the ventilator circuit.⁴⁰

Treatment Complications

Persistent or worsening hypoxemia suggests the development of a complication from mechanical ventilation. Complications that must be considered include right mainstem intubation, pneumothorax, gastric distention, endotracheal tube dislodgement, tube blockage, aspiration, bronchospasm, and ventilatory malfunction. Each of these must be considered and the patient reassessed after any intervention.

Cardiovascular Collapse and/or Pneumothorax

The two most fearsome complications of asthma include cardiovascular collapse and /or pneumothorax. Hypotension can be caused directly by the aforementioned auto-PEEP leading to essentially tamponade physiology: an increase in intrathoracic pressure leads to subsequent reduction in preload and a decrease in cardiac output. Removing the tube and pushing down on the chest to manually empty the lungs is the first step. If clinical signs of a tension pneumothorax are present (unequal breath sounds, tracheal deviation, subcutaneous emphysema), needle decompression should be performed followed by tube thoracostomy. Note that puncturing a hyperinflated lung during chest tube insertion can produce a rush of air similar to releasing a tension pneumothorax but will not improve ventilation.³⁶ In this case, the tube should be repositioned or another tube should be inserted. Standard fluid boluses are appropriate while the complications of auto-PEEP are being corrected. Practitioners should not forget that the more common cause of hypotension in the intubated asthmatic patient is medication-induced, including sedatives and NMBs.

WEANING

Weaning and extubation criteria have not been validated for patients with acute exacerbations of OLD. A recommended approach is to perform a spontaneous breathing trial in an

awake patient after Paco_2 has normalized, airway resistance is less than 20 cm H_2O , and neuromuscular weakness has not been identified. After extubation, observation in an ICU setting is recommended for an additional 12–24 hours. Once the patient is stable enough for discharge, patient education, systemic corticosteroids, and proper use of β -agonist therapy must be reinforced along with timely follow-up with a pulmonologist or his or her primary care provider to help prevent further exacerbations.

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Pulmonary Embolism

Ari Ciment • Lawrence M. Ciment

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INCIDENCE AND MORTALITY

Since the advent of CT pulmonary angiography, there has been a marked increase in the incidence of diagnosed pulmonary embolism (PE), from 62.1 to 112.3 cases per one hundred thousand, although it is still believed that more than half of all cases remain undetected. Concomitantly over the last 30 years, the incidence of pulmonary emboli in all hospitalized patients has tripled, from 0.5% to 1.5%.¹ Although the incidence of PE has increased markedly, the absolute mortality has not, suggesting a new over-diagnosis.^{2,3}

PATHOPHYSIOLOGY—RISK FACTORS

The pathogenesis of PE classically stems from Virchow's triad of endothelial injury, circulatory stasis and hypercoagulable state. Reversible risk factors include major factors such as surgery, hospitalization or plaster cast immobilization all within the prior month. Minor factors include estrogen therapy, pregnancy, prolonged travel > 8 hours and or the major factors when they occurred 1 to 3 months before VTE diagnosis.⁴ Newer epidemiologic studies in the last several years have interestingly focused on physical inactivity, steroids and even blood type as potential risk factors.⁵⁻⁷ In a study of 69,950 female nurses, PE risk was more than

doubled in women who were sedentary compared with those who were more active.⁵ A population based case control study in Denmark recently showed that systemic steroids increased venous thromboembolism (VTE) risk two-fold.⁶ Finally, VTE patients were 2.21 times more likely to have non-O blood type than their control counterparts.⁷ Notwithstanding these interesting findings, the most common reversible risk factor for PE remains obesity, followed by cigarette smoking and hypertension⁸ (Table 13-1). In view of the multiplicity of risk factors, updated models—such as the IMPROVE risk assessment model—have been developed to guide appropriateness of VTE prophylaxis in hospitalized patients⁹⁻¹¹ (Table 13-2).

PATHOPHYSIOLOGY—THROMBOPHILIA FOCUS

Genetic hypercoagulable states and acquired risk factors combine to establish an intrinsic risk of thrombosis for each individual. Inherited disorders are found in up to one-half of the patients who present with VTE before the age of 45 years, particularly those whose event occurred in the absence of provocative risk factors. The indications for thrombophilia screening are controversial. For patients with a first episode of VTE, thrombophilia screening is indicated if the results

 **TABLE 13-1: Risk Factors for Pulmonary Embolus⁴⁻⁸**

Major Risk Factors ^a	Minor Risk Factors (RFs)	Newly Proposed RFs
Surgery	Estrogen therapy	Physical inactivity
Hospitalization	Pregnancy	Steroids
Plaster cast immobilization	Prolonged travel > 8 hours	Non-O blood type
	Major RFs occurring 1–3 months prior	

^aThe reversible major risk factors apply when they occur within the prior month of VTE episode.

influence the duration of treatment or impact family counseling regarding use of estrogen-containing compounds.¹² It is reasonable to screen patients whose first episode of thrombosis occurred before the age of 45 years, those with recurrent thrombosis, particularly if unprovoked, and patients with thrombosis in an unusual site (such as cerebral or mesenteric veins) and those with 2 or more first-degree relatives with history of thrombosis.

It may also be reasonable to screen women with a history of 3 or more second-trimester pregnancy losses or an intrauterine death for lupus anticoagulant (LA) and anticardiolipin antibody (ACL). Screening typically includes functional assays for antithrombin and protein C, a free protein S level, testing for activated protein C resistance using the modified APC sensitivity ratio with DNA testing for the Factor V Leiden mutation if the screening test is equivocal, DNA testing for the prothrombin gene mutation, phospholipid-based clotting tests to detect LA, and enzyme immunoassay for ACL identification¹² (Table 13-3). Knowing the thrombophilia profile may help with strategizing anticoagulation dosing post PE. Whereas provoked PE generally entails 3 to 6 months of treatment and unprovoked PE necessitates lifelong therapy, there is a gray zone in which factors such as thrombophilia help individualize treatment. The “Gray Zone,” or indeterminate category described by Samuel Goldhaber, will lead to an individual treatment strategy that will consider past/family VTE history, gender, presenting symptoms of PE or deep vein thrombosis (DVT), recanalization of leg veins on ultrasound, hypercoagulability workup and patient preference¹³ (Table 13-4).

 **TABLE 13-3: Hypercoagulable Workup. Whom to Screen and What to Test for^{12,13}**

Whom to Screen	What to Test
1st episode < 45 yo	Factor V Leiden
Recurrent thrombosis	Antithrombin
Thrombosis in unusual site (cerebral or mesenteric)	Protein C/S
2 or more 1st degree relatives with history of thrombosis	Prothrombin gene mutation
Woman with 3 or more 2nd trimester pregnancy losses or intrauterine death	Lupus anticoagulant Anticardiolipin antibody

PATHOPHYSIOLOGY—PULMONARY AND HEMODYNAMIC EFFECTS OF ACUTE PE

Understanding both the pulmonary and hemodynamic effects of an acute PE has diagnostic and therapeutic implications. The most common mechanism of hypoxemia in PE is related to ventilation-perfusion mismatching. Unlike normal lungs, in which ventilation is well matched to blood flow, PE causes redistribution of blood flow so that some lung gas exchange units have low ratios of ventilation to perfusion, whereas other lung units have excessively high ratios of ventilation to perfusion.¹⁴ Total dead space increases because lung units continue to be ventilated despite diminished or absent perfusion. Whereas complete obstruction of a pulmonary artery by an embolus causes an increase in anatomic dead space, incomplete obstruction of a pulmonary artery increases physiologic dead space. Increased dead space impairs the efficient elimination of carbon dioxide. Medullary chemoreceptors that sense any increase in arterial P_{CO_2} , as well as possible local lung capillary sensors triggered by irritants, stimulate an increase in total minute ventilation. Therefore it is common for a patient with a PE to initially present with a low arterial P_{CO_2} on initial arterial blood gas. Hypercapnia, on the other hand, may reflect a massive embolism accompanied by marked increases in both anatomic and physiologic dead space. The subsequent severe reduction in alveolar volume of each tidal breath eventually results in an inability of the ventilatory muscles to sustain the marked increase of minute ventilation needed to maintain normal arterial $PaCO_2$ ¹⁴ (Table 13-5).

 **TABLE 13-2: Anticoagulation Risk Assessment Model^{*}**

Risk Factor	Prior VTE	Diagnosed thrombophilia	Current lower limb paralysis	Current Cancer	Immobilized for 7+ days	ICU/CCU stay	> 60 yrs of age	TOTAL
Points	3	2	2	2	1	1	1	12

^{*}The authors of IMPROVE set a total score of 0 and 1 as low risk and not needing anticoagulant prophylaxis and a score of 2 or more as appropriate for prophylaxis^{10,11}

 **TABLE 13-4: Duration of Anticoagulation after Venous Thromboembolism***

Type of VTE	Provoked	Indeterminate	Idiopathic
Treatment Strategy	3–6 months of anticoagulation	Individualize therapy	Possibly indefinite anticoagulation

*Optimal duration of anticoagulation after venous thromboembolism depends on whether it was provoked or idiopathic. If not clear, should individualize treatment strategy.¹³

From a cardiovascular perspective, hypoxemia causes pulmonary vasoconstriction. Sustained elevated pulmonary artery pressure translates into right ventricular wall stress. RV pressure effects on the right coronary artery lead to diminished subendocardial perfusion with ensuing limited myocardial oxygen supply. Microinfarctions lead to troponin elevations and RV overload causes elevation of BNP and PRO-BNP.^{15,16} Although the elastic nature of the pulmonary arteries may dampen PAP increases, PAP typically doubles (to roughly 40 mm Hg) in an acute PE. RV enlargement attributable to pressure overload causes a leftward shift of the interventricular septum, demonstrating interventricular dependence, which ultimately can result in decreased cardiac output with ensuing shock¹⁷ (Figure 13-1).

SYMPTOMS OF PULMONARY EMBOLISM

The clinical manifestations/symptoms of pulmonary embolus as derived from the data from PIOPED II, include dyspnea at rest or with exertion (73%), pleuritic pain (44%), calf or thigh pain (44%), calf or thigh swelling (41%), cough (34%), > 2-pillow orthopnea (28%, and wheezing (21%). The onset of dyspnea is usually rapid: 46% within seconds and 26% within minutes. The most common signs were tachypnea (54%), tachycardia (24%), rales (18%), decreased breath sounds (17%), an accentuated pulmonic component of the second heart sound (15%), and jugular venous distension (14%).¹⁸ Signs of a massive PE include increased jugular venous pressure, a right-sided S3, and a parasternal lift, but circulatory collapse is uncommon (8%). Interestingly, dyspnea may be absent even in patients with circulatory collapse.

Symptoms or signs of lower extremity DVT were found in roughly half of PE patients and included edema, erythema, tenderness, or a palpable cord in the calf or thigh.¹⁸ However, pulmonary embolism is frequently asymptomatic. Silent pulmonary embolism was diagnosed in 1665 of 5233 patients (32%) with DVT in a recent systematic review of 28 DVT studies.¹⁹

DIAGNOSTIC ALGORITHM AND CLINICAL PROBABILITY ASSESSMENT

When a PE is suspected, the first task is clinical probability assessment. Bayes theorem states that posttest odds equal the likelihood ratio for test result multiplied by pretest odds. The PE probability assessment tests focus on risk factors, symptoms and signs. The most prevalent tests include the Wells model and Revised Geneva Score (Table 13-6).

The algorithm derived from the European Society of Cardiology and from the PIOPED II investigators proceeds from there in the following manner: If the Wells score is < 7 or RGS < 11, a PE is unlikely and a d-dimer can definitively rule out a PE. However, if the Wells score is > 7 or RGS > 11, a CT pulmonary angiogram (CTPA) needs to be done to rule out a PE.^{24,25} *The Clinical Policy Guidelines published in the Annals of Emergency Medicine*, on the other hand, has a much lower threshold to necessitate a CTPA to rule out a PE using a cutoff Wells of > 3 and RGS > 3.²⁶

D-DIMER, CT-PULMONARY ANGIOGRAM AND V/Q SCANNING

Measurement of plasma d-dimer allows PE to be ruled out when clinical suspicion is low or moderate, but interpretation is complicated by the fact that d-dimer levels normally rise

 **TABLE 13-5: Potential Gas Exchange Abnormalities in Acute PE¹⁴**

Gas Exchange Abnormalities in Acute PE	Mechanism
Respiratory alkalosis from hyperventilation	Medullary chemoreceptors that sense any increase in arterial Pco ₂ , as well as possible local lung capillary sensors triggered by irritants, stimulate an increase in total minute ventilation
Areas of Ventilation/Perfusion < 1.0: Low V/Q	Impaired oxygen transfer to pulmonary capillaries with preserved blood flow, that is, atelectatic areas of lung and/or shunted blood from other obstructed capillaries leading to a local mismatch phenomenon. <i>Extreme example:</i> Right to left shunt: If there is preserved flow but no ventilation, blood will go to left heart without any oxygenation
Areas of Ventilation/Perfusion > 1.0: High V/Q	Ventilation to gas exchange areas exceeds capillary blood flow, that is, obstructed blood vessel direct effect → Physiologic dead space. <i>Extreme example:</i> Anatomic dead space: If there is no capillary blood flow, then it becomes anatomic dead space as no breathed gas enters gas exchange units

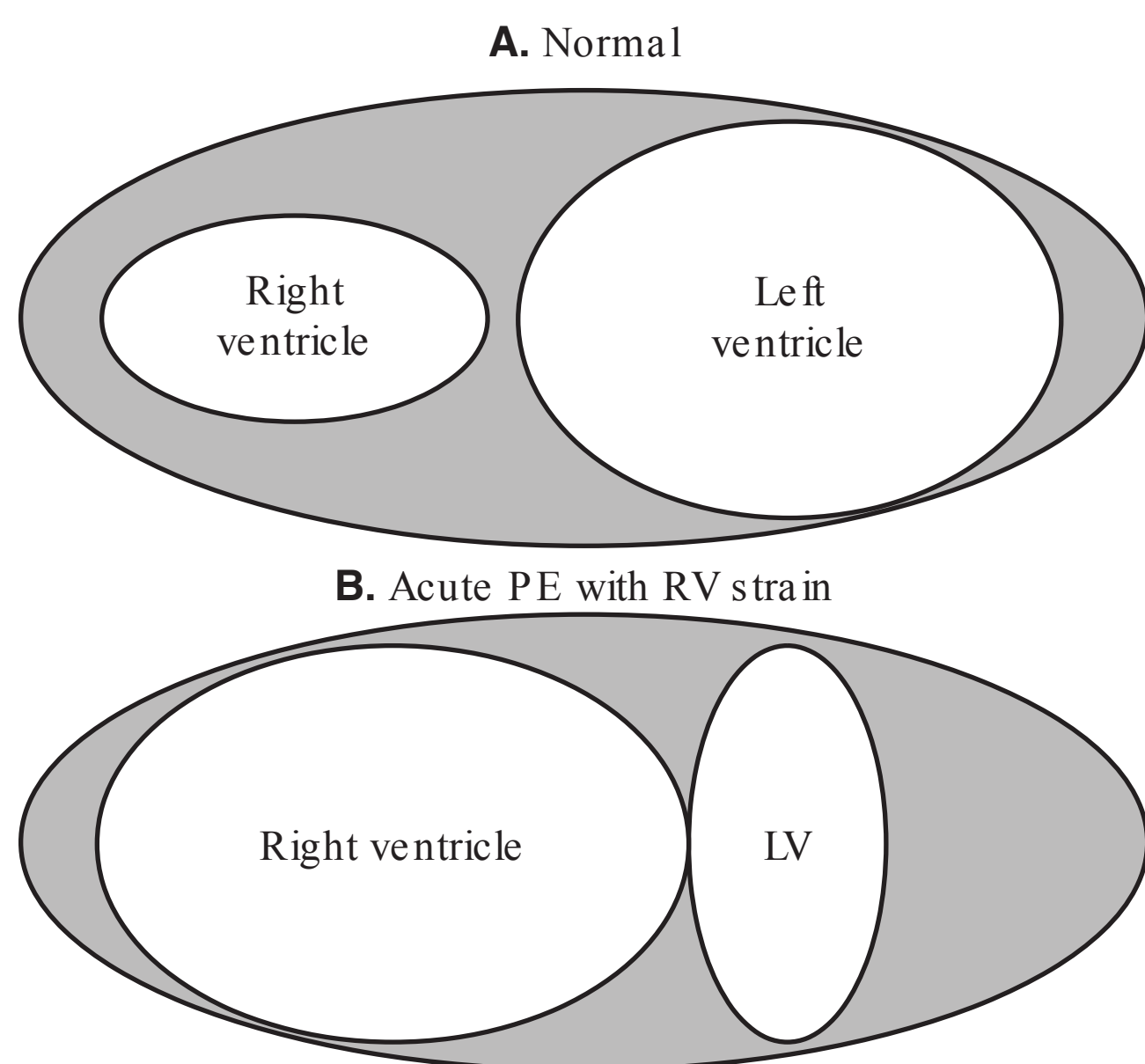


FIGURE 13-1 Ventricular interdependence in RV failure. **A.** Normal representation of heart chambers, right and left ventricles. **B.** Representation of heart chambers during an acute pulmonary embolism with right heart strain. Dilatation of the RV shifts the interventricular septum toward the left, changing LV geometry. These changes may contribute to low cardiac output state by decreasing LV distensibility, preload, and ventricular elastance.¹⁷

with age. In a recent multicenter European study, investigators prospectively evaluated the accuracy of an age-adjusted d-dimer cutoff in 2898 patients with low or moderate clinical probability for PE. A d-dimer result was considered negative if it was less than $\text{age} \times 10$ for patients aged 50 and older while, for younger patients, the cutoff was fixed at 500 $\mu\text{g/mL}$. Patients with a positive result underwent CTPA. All patients were followed for 3 months. Of 331 patients 50 and older with d-dimer levels between 500 $\mu\text{g/mL}$ and their age-adjusted cutoff, only one (0.3%) was found to have PE

during follow-up. The use of the age-adjusted cutoff resulted in a 12% absolute increase and a 41% relative increase in the proportion of negative d-dimer results.²⁷

The sensitivities of CTPA have been > 90% for the diagnosis of PE dating back to the Prospective Investigation of Pulmonary Embolism Diagnosis II (PIOPED II) study.²⁸ Higher sensitivities > 96% are reported when CTPA is combined with a moderate to high clinical probability assessment for PE, but lower for those with a low suspicion for PE. Regarding the false negative rate: Among the 1481 untreated patients in whom PE was excluded by CTPA in the recent ADJUST-PE study, there was one DVT (0.1%), four cases of nonfatal PE (0.2%), and two indeterminate events in three-month followup.²⁷

Although the risk of missing a PE in those with a negative CTPA and a high clinical suspicion for PE has been estimated as high as 5%, it is crucial to point out that over the past 10-15 years, scanners have become more technically advanced and the false-negative rates have only improved.²⁹

V/Q scanning is utilized if CT is unavailable, if there is renal failure, a contrast allergy or very rarely when trying to confirm a negative PE in lieu of a high clinical probability and negative CTPA. The sensitivity is reportedly 77.4% and specificity is 97.7%.³⁰

RADIOLOGIC TESTING INCLUDING DURING PREGNANCY

If a PE is suspected during pregnancy, the algorithm starts with a d-dimer and a venous ultrasound. If the d-dimer is negative, further radiation and its potential fetal risk may be avoided. If the venous ultrasound is positive, the need for further testing is also obviated. If it is negative, then a V/Q scan is next unless the CXR has baseline abnormalities, in which case a CTPA should be done. Clinical Practice Guidelines from the American Thoracic Society (ATS) removes d-dimer from the pregnant PE algorithm³¹ (Table 13-7).



TABLE 13-6: Well versus Geneva Scoring System*

Wells Clinical Probability Assessment

Risk Factors:

- Previous VTE (+ 3 points)
- Immobilization or surgery within month (+ 1.5 points)
- Malignancy (+ 1.0 point)

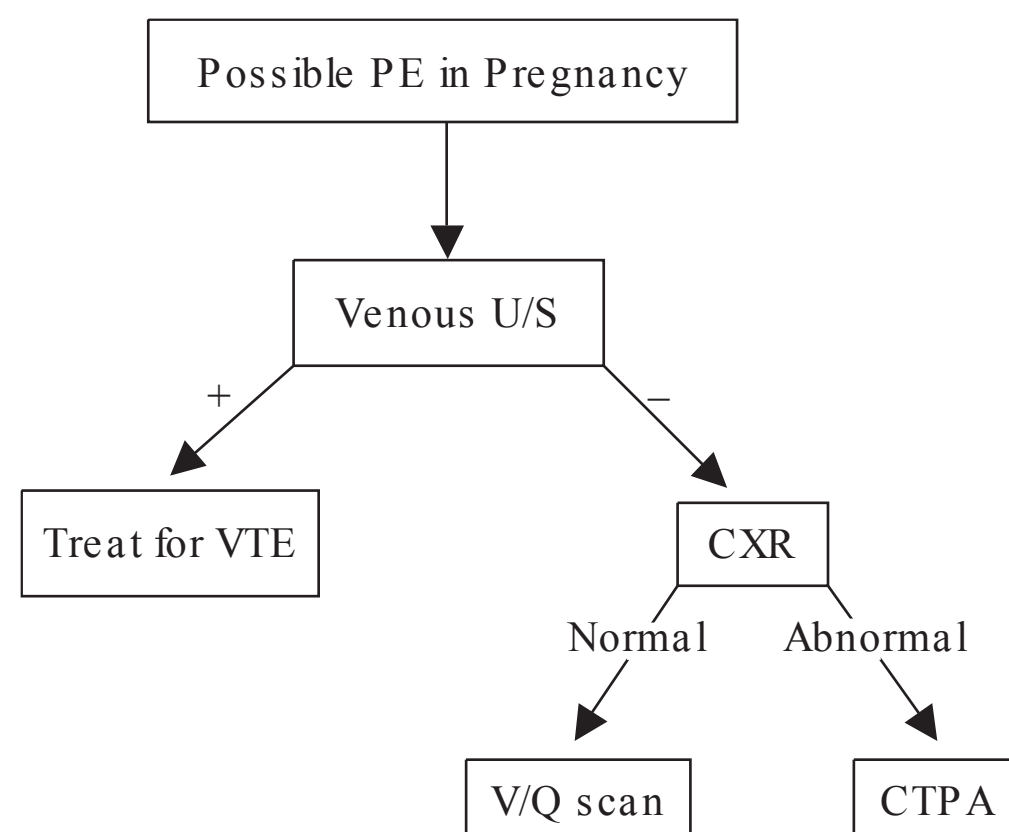
Signs and Symptoms:

- Signs and symptoms of DVT (+ 3 points)
- Hemoptysis (+ 1 point)
- HR > 100 (+ 1.5 points)
- Alternate diagnosis is less likely than PE (+ 3 points)

Revised Geneva Clinical Prediction Model

- Age > 65 (+ 1 point)
- Previous VTE (+ 3 points)
- Surgery or fracture within month (+ 2 points)
- Active malignancy (+ 2 points)
- Unilateral leg pain (+ 3 points)
- Hemoptysis (+ 2 points)
- HR 75–94 (+ 3 points)
- HR > 95 (+ 5 points)

*The Wells clinical probability assessment tool compared with the Revised Geneva Score (RGS). They are both based on signs, symptoms and historical variables.^{20–23} A Wells score < 4 is unlikely PE and > or = 4 is likely PE on the 2-Level score but Wells score > or = 7 separates low/intermediate groups from high probability on the original three-tier classification system. An RGS of 0–3 is low clinical probability, 4–10 is intermediate and > or = 11 is high probability.


TABLE 13-7: Algorithm for Pregnant Patient Suspected to Have Pulmonary Embolus


Data from ATS clinical practice guidelines from 2011.

Regarding safety of radiologic tests in pregnancy, the upper limit of teratogenic injury to the fetus is considered to be 50 mSv (50 000 mGy), and all radiologic tests fall well below this limit. CTPA radiation dose delivered to the fetus is lower than that of perfusion lung scintigraphy in the first or second trimester but perfusion lung scintigraphy is also a reasonable option with a solid diagnostic yield (75%) and less radiation to the maternal breasts.³¹

Risks of CTPA include contrast injuries, incidentalomas, radiation exposure and overdiagnosis leading to over-treatment. Renda Wiener et al. demonstrated that despite an increased incidence of PE diagnoses since CTPA was introduced in 1998, the mortality remained leveled while anticoagulation complications have increased by roughly 5%.² This suggests overdiagnosis and reminds us that PE treatment

is not without risk, and small peripheral PE picked up on CTPA may actually not need such aggressive treatment. As for radiation risk, there is roughly 10 mSv per CTPA. A total of 620 40-year-old females having a CTPA would potentially lead to the development of 1 radiation-induced cancer.³²

Radiologic follow-up tests post PE treatment are controversial. In fact, venous ultrasounds remain abnormal 42% of the time and chest CT stays abnormal 57% of the time 1 year later. Therefore, routine follow-up ultrasounds and CT scans are not recommended to help determine the optimal anticoagulation duration.³³

MORTALITY RISK ASSESSMENT/ PROGNOSTIC SCORING

Mortality risk assessment in PE is used to help anticipate which patients may require advanced monitoring or even thrombolysis. Registries, such as the ICOPER, have shown that the 3-month mortality rates of hemodynamically unstable patients were roughly 4 times worse than the hemodynamically stable (59% versus 15%).³ But even amongst the hemodynamically stable patients, certain clinical predictors can be teased out to help prognosticate and perhaps treat more aggressively. The Geneva Prognostic Score and the Pulmonary Embolism Severity Index (PESI) contain historical and physiologic variables such as cancer, heart failure, previous DVT, SBP, and HR (Table 13-8).^{34,35} A study by Jimenez et al in 2007 analyzing 30 day mortality in 599 PE patients showed an OR of 4.5 for PESI class V and an OR of 3.1 for Geneva high risk.³⁶

Absent on those classic prognostic scoring tests, however, are the variables that signify RV dysfunction (RV/LV ratio, troponin and natriuretic peptide elevation). Recent studies and scoring systems such as the PREP score have incorporated echocardiography findings such as the RV/LV ratio and BNP into a prognostic score.³⁷


TABLE 13-8: Comparison of Geneva Prognostic Score (GPS) to the Pulmonary Embolism Severity Index (PESI)

Geneva Prognostic Scale (variables)	Points	Pulmonary Embolism Severity Index (variables)	Points
Cancer	2	Age > 80 ^a	Age in years
Heart failure	1	Male	10
Previous DVT	1	Cancer ^a	30
SBP < 100	2	Heart failure	10
PaO ₂ < 60 mm Hg	1	Chronic lung disease ^a	10
DVT by ultrasound	1	HR > /= 110 ^a	20
		SBP < 100 ^a	30
		RR > /= 30	20
		Temperature < 36°C	20
		Altered mental state	60
		O ₂ sat < 90% ^a	20

A score of 3 or more on the GPS defines high risk for adverse outcomes. A score of 90 or more on the original PESI indicates high risk for adverse outcomes. Of note, any one of the variables marked by an asterisk would be enough to be classified as higher risk (at least 8.9% 30-day mortality) in simplified PESI.^{30,31}

Nearly 1/3 of hemodynamically stable patients have echo demonstration of RV dysfunction, 10% of whom subsequently deteriorate.³⁸ Two large studies showing RV hypokinesis in hemodynamically stable patients have shown mortality rates are twofold in this population.^{3,39} RV/LV ratio > 0.9 on CTPA has also been shown to be a significant negative prognostic factor.⁴⁰ Natriuretic peptide elevations (BNP > 500 pg/mL and NT-PBNP) are also present in 1/3 of PE patients, and a large meta-analysis has shown that this finding carried a 6-fold likelihood of adverse clinical outcomes.⁴¹ Troponin elevations (troponin I > 0.4 ng/mL) likewise have proven to be negative prognostic markers. In a recent meta-analysis of 20 studies and 1985 patients, the odds ratio for death resulting from PE was 9.44 in those with elevated troponins.⁴²

TREATMENT STRATEGIES

Three Major Types and Their General Approaches

Essentially, there are 3 main types of patient clinical presentations of PE to an ED or ICU⁴³ 1) “Submassive PE”- hemodynamically stable; (2) “Submassive PE”- hemodynamically stable with respiratory compromise and/or echocardiographic RV dysfunction; and (3) “Massive PE”- hemodynamically unstable with SBP< 90 for > 15 minutes. Depending on the presentation, a treatment strategy is chosen. The hemodynamically stable patient is typically treated with an anticoagulant alone while the “Massive PE” patient should be anticoagulated and fibrinolyzed if no contraindications. The management of this second category, a submassive PE patient with either respiratory or hemodynamic instability, is a controversial matter. Some would choose basic anticoagulation, others would advocate systemic thrombolysis, and yet others would pursue localized direct thrombolysis +/- ultrasound therapy (Table 13-9).

Initial Treatment Usually Coupled with Longer-Term Plan of Action to Prevent Recurrent VTE

Concomitant with the initiation of acute PE treatment is consideration of the likely duration of such treatment to prevent

recurrent PE. The duration determination will depend on the likelihood of recurrent VTE which in turn depends on whether the PE was “provoked” or “unprovoked.” “Provoked” means there was exposure to known risk factors triggering the thrombotic episode while “unprovoked” cases have no obvious historical precipitant. Provoked PE patients will typically require 3–6 months of therapy, whereas the unprovoked PE patients may need indefinite therapy. The “Gray Zone” as described by Dr. Sam Goldhaber is a scenario in which it is not clearly provoked or unprovoked. In such a situation, consideration of past/family VTE history, gender, recanalization of leg veins on U/S, hypercoagulability and patient preference will help determine the clinician’s duration recommendation (Table 13-4).

Initial treatment for PE, which typically includes anticoagulation +/- thrombolysis, is followed by long-term treatment, which usually includes the Vitamin K antagonist warfarin and/or the newer oral factor Xa inhibitors. A study of 326 patients in 2003 demonstrated that for PE patients *with* reversible risk factors, 3 months of therapy was no worse than extending treatment to 6 months.⁴⁴ On the other hand, for PE scenarios *without* clear provocation, some form of anticoagulation beyond 6 months, even if not fully above classical therapeutic levels (i.e., INR > 2.0), is better than nothing in preventing recurrent VTE. For instance, in patients with idiopathic VTE after 6 months of full dose anticoagulation (INR > 2), placebo was compared with low-dose warfarin (INR 1.5–2.0). The placebo group had 7.2 VTE events per 100 person-years versus 2.6 per 100 person-years.⁴⁵ Similarly, the WARFAS investigators compared aspirin to placebo in the seminal “Aspirin for Preventing the Recurrence of VTE” trial in 2012.⁴⁶ Patients with first ever unprovoked VTE who had completed 6 to 18 months of anticoagulant therapy were assigned to 100 mg of aspirin or placebo for 2 years. Although the conclusion that aspirin offered some VTE protective effect has been challenged, once again this study also highlighted the significant VTE recurrence rate in patients not treated for an unprovoked VTE, which is roughly 20% within 2 years.⁴⁷

PE Strategies: UFH, LMWH and Direct Thrombin Inhibitors

Initial PE treatment classically includes unfractionated heparin (UFH), low molecular weight heparin (LMWH), thrombolysis, percutaneous mechanical embolectomy, and even

TABLE 13-9: Fibrinolysis in Submassive PE*				
Submassive PE with RV Strain- Shock or Respiratory Failure Plus Moderate to Severe RV Strain				
Shock	Any hypotension (SBP < 90)	Shock Index (HR > SBP) > 1		
Respiratory failure	O ₂ saturation < 95%	Borg score > 8	Altered mental status	Appearance of suffering
Moderate to severe RV strain	RV hypokinesis or RVSP > 40	Troponin above borderline value	BNP > 100 pg/mL or ProBNP > 900 pg/mL	

*Submassive PE without RV strain typically will get anticoagulation alone and massive PE (SBP < 90 for > 15 min) typically will get fibrinolysis if no contraindications. Possible fibrinolysis (Alteplase 100 mg IV/2 hours) candidate if shock or respiratory failure along with moderate to severe RV strain.



TABLE 13-10: Adjustment of IV Unfractionated Heparin Based on Activated Partial Thromboplastin time^{25,45}

Activated Partial Thromboplastin Time	Change of Dosage
< 1.2 times control	80 U/kg bolus; increase infusion rate by 4 U/kg/h
1.2–1.5 times control	40 U/kg bolus; increase infusion rate by 2 U/kg/h
1.5–2.3 times control (46–70 seconds)	No change
2.3–3.0 times control	Reduce infusion rate by 2 U/kg/h
> 3.0 times control	Stop infusion for 1 h, then reduce infusion rate by 3 U/kg/h

surgery. After briefly describing some studies regarding heparin and the more usual LMWHs, we will review some of the newer studies regarding the novel Factor Xa inhibitors and direct thrombin inhibitors.

The earlier the anticoagulation was started in acute PE, the lower the mortality. This was highlighted by a study from 2010 analyzing 400 consecutive patients with acute PE: those who received heparin in the ED compared with those heparinized post admission had a 4.4% versus a 15.3% 30-day mortality.⁴⁸ The heparin nomogram (Table 13-10) established in 1996 remains universally applied.^{25,49}

LMWHs include enoxaparin, dalteparin, tinzaparin and fondaparinux. Advantages of LMWH versus heparin include reduced risk of bleeding, predictable pharmacokinetics allowing weight-based dosing without the need for monitoring, and a reduced risk of heparin-induced thrombocytopenia and/or osteoporotic fractures.²⁵ Comparing UFH and LMWH, a large meta-analysis in 2004 demonstrated no significant difference between the two in terms of recurrent symptomatic venous thromboembolism, excessive bleeding, or death at the end of the trial.⁵⁰

The LMWH dalteparin, as demonstrated by the CLOT investigators in 2003, was statistically superior to Coumadin in preventing VTE recurrence compared with warfarin in cancer patients.⁵¹ LMWH is also safe and effective in pregnancy as either prophylaxis or treatment.⁵² The PROTECT trial in 2011 failed to show superiority of LMWH over UFH in preventing proximal DVT in critically ill patients.⁵³

Some of the key more recent studies include those focused on Factor Xa inhibitors fondaparinux (Arixtra), rivoraxaban (Xarelto), apixaban (Eliquis) and edoxaban (Lixiana).

The MATISSE Investigators in 2003 showed a similar 3-month recurrent VTE incidence for fondaparinux compared with UFH (3.8% vs 5%) in a 2003 study.⁵⁴ The EINSTEIN investigators in 2010 demonstrated that rivoraxaban was noninferior to enoxaparin-warfarin for symptomatic VTE, paving the way for a simple, single-drug approach.⁵⁵ The subsequent EINSTEIN-PE study in 2012 was an intention-to-treat RCT that showed a similar rate of recurrent VTE (2.1% vs. 1.8%) in the rivoraxaban versus standard enoxaparin-VKA regimens but had significantly less incidence of major bleeding (1.1% vs. 2.2%).⁵⁶

The AMPLIFY-EXT investigators studied apixaban for extended treatment of VTE. Patients with VTE who completed 6 to 12 months of anticoagulation and for whom

there was clinical equipoise regarding continuation or cessation of anticoagulation were studied. Recurrent VTE occurred within 12 months in 8.8% of the placebo group compared with 1.7% in the apixaban group. There was no increased risk of major bleeding as well.⁵⁷ In the Oral Apixaban for Treatment of Acute VTE study, the investigators compared apixaban with conventional therapy (subcutaneous enoxaparin, followed by warfarin) in 5395 patients with acute VTE. Fixed-dose apixaban was just as effective as enoxaparin-warfarin but was associated with significantly less bleeding (composite outcome of major bleeding and clinically relevant nonmajor bleeding was 4.3% in the apixaban group vs. 9.7% in the conventional group).⁵⁸

Finally, the HOKUSAI-VTE investigators compared edoxaban (3 to 12 months of treatment after initial heparin anticoagulation) versus warfarin in 4921 VTE patients. Edoxaban was noninferior in terms of recurrent VTE and was associated with significantly less bleeding. Perhaps most intriguing, of the 938 patients (28% of all PE patients) with RV dysfunction, as assessed by measurement of NT-PBNP, the rate of recurrent VTE was 3.3% versus 6.2% in the warfarin group.⁵⁹

Summarizing the aforementioned studies' key points: fondaparinux is as effective as UFH in initial PE. Rivoraxaban is noninferior to enoxaparin-warfarin regimens to prevent recurrent VTE and PE and has significantly less bleeding. Apixaban also is safe and effective for acute and extended VTE treatment and has a good bleeding profile. Edoxaban is an alternative to warfarin and may be especially suited for those presenting with signs of RV dysfunction.

Dabigatran, a direct thrombin inhibitor approved for stroke prevention in nonvalvular atrial fibrillation, was studied by the RE-COVER study group. After initial parenteral anticoagulation for acute VTE, patients were randomized to either dabigatran or warfarin. Like the factor Xa inhibitors, there is no monitoring for therapeutic levels. Dabigatran proved noninferior to warfarin in terms of 6-month VTE recurrence rate as well as safety, although there were more "adverse events leading to discontinuation of the study drug" versus warfarin.⁶⁰ Dabigatran is the first of the novel oral anticoagulants (NOACS) to have an FDA approved reversal agent.⁶¹ The reversal agent for Rivoraxaban and Apixaban, Andexanet Alfa, reversed the anticoagulant activity of apixaban and rivoroxaban in older healthy participants within minutes but is not yet FDA-approved.⁶² In the latest 2016 evidence-based guideline, Antithrombotic Therapy for VTE



TABLE 13-11: Key Drugs used in Venous Thromboembolism

Drug Type, Name	Key Studies/Year	Key Findings
LMWH		
Dalteparin (Fragmin)	CLOT/2003 ⁴⁷	Dalteparin superior to Coumadin in cancer pts
Fondaparinux (Arixtra)	MATISSE/2003 ⁵⁰	Similar to heparin for VTE recurrence
Rivoraxaban (Xarelto)	EINSTEIN-PE/2012 ⁵²	Similar to enoxaparin-VKA in recurrent VTE and less major bleeding
Apixaban (Eliquis)	AMPLIFY/2013 ⁵⁴	Similar to enoxaparin-VKA in recurrent VTE and less major bleeding
Edoxaban (Lixiana)	HOKUSAI-VTE/2013 ⁵⁵	Noninferior to heparin/VKA in terms of recurrent VTE, less bleeding, and 1/2 recurrent VTE in RV dysfunction group compared with heparin/VKA
Direct thrombin inhibitor		
Dabigatran (Pradaxa)	RE-COVER/2009 ⁵⁶	Noninferior to warfarin in 6 month VTE recurrence
Fibrinolytics		
Alteplase (tPA)	Pulmonary Embolism-3 Trial/2002 ⁶⁰	Alteplase may help for submassive PE
Tenectaplaste	PEITHO/2014 ⁶⁴	Tenectaplaste may help for submassive PE but risk-benefit ratio best if less than 75

Disease: CHEST Guideline, from the American College of Chest Physicians, experts now recommend Non-vitamin K antagonist oral anticoagulants (NOACs) over warfarin for initial and long-term treatment of VTE in patients without cancer.⁶³ (Table 13-11).

PE Strategies: Fibrinolytics

Available fibrinolytics, or “clot-busters,” in 2014 include streptokinase, urokinase, alteplase, reteplase and tenectaplaste. Alteplase, or tPA, is given as a 100 mg infusion over 2 hours, whereas the newer tenectaplaste is given as an IV bolus in just 5 seconds. Fibrinolytics have classically been used for the PE patients with hemodynamic instability (i.e., massive PE with SBP < 90 for 15 minutes). There is just one randomized control trial from 1995 comparing heparin alone with thrombolysis in massive PE patients.⁶⁴ The 4 patients in the heparin-alone group died, while the 4 patients in the streptokinase group survived.

Although the use of fibrinolytics in submassive PE has not been demonstrated to have an advantage over conventional treatment, trials in “major PE” have shown significantly less recurrence or death (9.4% vs 19%).^{65,66} The meta-analysis when comparing thrombolysis versus heparin, also showed a significant rate of nonmajor bleeding only (22.7% vs. 10%) with only a trend toward major bleeding along with a non-significant increase of intracranial hemorrhage in the thrombolysis group.

The next order of business has been to tease out those patients with “major PE,” other than those with massive PE, who may benefit from thrombolysis. Reviewing registry data, while massive PE patients given lytic therapy have improved mortality rates, the submassive PE population overall actually had typically worse mortality rates when given thrombolytics. In fact, a recent retrospective cohort study of 15944 patients

from the RIETE (Registro Informationdo de la Enfermedad TrombEmbolica) registry concluded that in normotensive patients with acute PE, thrombolytic therapy was associated with a higher risk of death than no thrombolysis.⁶⁷

Since the short-term mortality rate for anticoagulated submassive PE patients is less than 3%, showing an effect from thrombolysis on this population would be very difficult and secondary outcomes such as persistent RV dysfunction or impaired quality of life (i.e., walking distance) represent surrogate goals of therapy. To this end, while fibrinolysis may decrease the mean PAP acutely by almost 10 mmHg compared to heparin, the several-month follow-up comparison generally shows an even more impressive roughly 2-fold decrease in PAP in those thrombolysed. For instance, the mean change from baseline PASP to follow-up PASP in the heparin-alone group was 32 +/- 12 to 24 +/- 9 while the change in the thrombolysis group was 43 +/- 12 to 20 +/- 7.⁶⁶

The Pulmonary Embolism Thrombolysis trial compared thrombolysis with tenecteplase and placebo in normotensive patients with confirmed PE, an abnormal right ventricle on echo or CT and a positive troponin I or T.⁶⁸ Both treatment groups (506 tenecteplase and 499 placebo) received standard anticoagulation. The primary endpoint was composite of death from any cause or hemodynamic collapse within 7 days of randomization; safety outcomes included ischemic/hemorrhagic strokes and other major bleeding episodes. The primary endpoint favored the tenecteplase group (2.6% vs. 5.6%), once again driven by the “hemodynamic collapse” (1.6% vs. 5%) variable as opposed to “all-cause mortality” (1.2% vs. 1.8%) alone.

Major non-intracranial bleeding (6.3% vs. 1.5%) as well as hemorrhagic plus ischemic strokes (2.4% vs. 0.2%) occurred significantly more in the tenecteplase group. In patients less than 75 years old, there was a 67% reduction in primary

endpoint concomitant with a 1.1% risk of stroke, while in those greater than 75 years old, there was only a 37% reduction in primary endpoint along with a 2% risk of stroke. Some believe that the results of PEITHO justify the concept of risk stratification of normotensive patients with acute PE and confirm that early “advanced” treatment prevents clinical deterioration in those with RV dysfunction and myocardial injury. But benefits did come at the cost of increased major bleeding, including intracranial hemorrhage. Patient’s age should be taken into account when weighing the thrombolysis risk-benefit ratio.

Contraindication to fibrinolysis, largely derived from the contraindications when used for myocardial infarction, might become relative in a patient with immediately life-threatening high-risk PE, and the clinician is in the best position to judge the relative merits on a case-by-case basis. Absolute contraindications include hemorrhagic stroke at any time, ischemic stroke within the previous 6 months, CNS damage or neoplasms, recent major trauma/surgery/head trauma (within previous 3 weeks), GI bleeding within the last month and known bleeding. Relative contraindications include refractory hypertension (SBP > 180 mmHg), advanced liver disease, and so on.²⁵

The AHA Scientific Statement on the management of PE suggested an aggressive approach for the patients with submassive PE and RV strain as long as there was (1) evidence for either shock (any SBP < 90, shock index > 1.0) or respiratory failure (SaO₂ < 90 with Borg score > 8 or altered mental status or appearance of suffering) or (2) moderate to severe RV strain (RV hypokinesis on echo or RVSP > 40 mm Hg or clearly elevated troponin above borderline, BNP > 100 pg/mL or PBNP > 900 pg/mL). If no contraindications to fibrinolysis, the authors recommended systemic alteplase 100 mg IV infusion over 2 hours.⁴³

PE Strategies: Interventional Therapies and Surgical Embolectomy

Interventional therapies with localized thrombolysis and ultrasound have gained momentum as technology has advanced. Catheter embolectomy techniques include thrombus fragmentation (i.e., rotation of pigtail catheter), rheolytic thrombectomy; high-pressure saline jet generating a pressure gradient enabling removal of thrombus fragments (i.e., AngioJet), suction thrombectomy (i.e., Aspirex catheter), and the classical conventional catheter-directed thrombolysis which typically employs 0.5–2 mg per hour per catheter for less than 24 hours with bolus doses between 2 to 5 mg.

Catheter-directed thrombolysis has recently been combined with ultrasonic energy to help synergize the t-PA effect. One such endovascular device, EKOS, transmits high-frequency, low-power sound waves. The energy causes fibrin strands to thin, exposing plasminogen receptor sites, which makes the thrombus more permeable, allowing the lytic to penetrate deeper. The SEATTLE II study is set to determine if the EKOS device will decrease the ratio of RV to LV diameter within 48 ± 6 hours in patients with massive or submassive PE when used in conjunction with recombinant t-PA as a treatment for acute PE. Fifty-nine patients with acute main or

lower lobe pulmonary embolism and echocardiographic RV/LV ratio ≥ 1.0 were studied in a recent multicenter randomized controlled trial comparing whether ultrasound-assisted catheter-directed thrombolysis (USAT) was superior to anticoagulation alone in the reversal of RV dilatation in intermediate-risk patients. The mean decrease in RV/LV ratio from baseline to 24 hours was 0.30 ± 0.20 in the USAT group versus 0.03 ± 0.16 in the heparin-alone group ($P < 0.001$).⁶⁹

A recent meta-analysis has demonstrated an 86.5% clinical success rate versus a 2.4% major complication rate when modern IR techniques are employed to treat massive PE.⁷⁰ In a 2005 report, 47 patients underwent surgical embolectomy in a 4-year period for massive and some submassive PE patients, with a 96% survival rate.⁷¹ The authors suggested consideration of surgical embolectomy not only in cases of failed medical therapy but also in hemodynamically stable patients with large central clot burden and documented RV dysfunction. Nevertheless, in most cases and institutions, surgical embolectomy should be considered (1) in massive PE when contraindications preclude thrombolysis; (2) for those who require surgical excision of a right atrial thrombus or paradoxical embolism; and (3) for rescuing patients whose condition is refractory to thrombolysis.⁴³ The AHA statement Class IIb recommendation with Level of Evidence C is that either catheter embolectomy or surgical embolectomy may be considered for patients with submassive acute PE judged to have clinical evidence of adverse prognosis (new hemodynamic instability, worsening respiratory failure, severe RV dysfunction, or major myocardial necrosis).

Some PE patients will develop chronic thromboembolic pulmonary hypertension (CTEPH) and some authors suggest obtaining a 6-week post PE echo to screen for persistent pulmonary hypertension that may predict this development.⁴³ CTEPH patients are chronically symptomatic, and typically have had large PEs in their younger age. The pathology of CTEPH is usually “type 2 disease” (40% of cases) characterized by intimal thickening and fibrosis with or without organized thrombus proximal to segmental pulmonary arteries. This pathology explains why definitive treatment of CTEPH entails surgical thromboendarterectomy rather than medical therapy, which is essentially ineffective.⁷²

PE Strategies: IVC Filters

Inferior vena cava (IVC) filter placement for the treatment of an acute PE and the prevention of recurrent PE has become more and more popular, perhaps coincident with more involvement of surgical and interventional radiology teams with PE therapy. Indications for IVC filter placement is primarily in a PE patient with contraindications to anticoagulation and/or with active bleeding. Complications associated with IVC filter placement include device malposition (1.3%), pneumothorax (0.02%), hematoma (0.6%), air embolism (0.2%), inadvertent carotid artery puncture (0.04%), and arteriovenous fistula (0.02%). The most frequent early complication occurs after sheath removal and manifests as access-site thrombosis (8.5%) of the common femoral vein.

Late complications of IVC filter placement include recurrent DVT (21%), IVC thrombosis (2% to 10%), IVC penetration (0.3%), and filter migration (0.3%)

Both permanent and retrievable IVC filters are currently used. The PREPIC Trial (Prévention du Risque d'Embolie Pulmonaire par Interruption Cave) randomized 400 patients with proximal DVT at high risk for PE in a 2-by-2 factorial design to receive UFH versus LMWH, with or without an IVC filter. The primary efficacy outcome was objectively documented PE at 8 years. Recurrent DVT, death, and major bleeding were also analyzed at 12 days, 2 years, and 8 years. All patients received parenteral anticoagulation for 8 to 12 days and vitamin K antagonists for at least 3 months, with 35% of patients in both groups receiving long-term oral anticoagulation. IVC filters significantly reduced the incidence of recurrent PE at 12 days (1.1% versus 4.8%, $P = 0.03$) and at 8 years (6.2% versus 15.1%, $P = 0.008$); however, IVC filters were associated with increased incidence of recurrent DVT at 2 years (20.8% versus 11.6%, $P = 0.02$).

There were no differences in major bleeding, post-thrombotic chronic venous insufficiency, or death during the study period. The beneficial effects of IVC filters to prevent recurrent PE in patients with DVT at high risk for PE were offset by an increased incidence of recurrent DVT with no effect on overall mortality.^{73,74} The recent PREPIC-2 randomized trial compared 200 patients with acute PE that received a retrievable IVC filter plus anticoagulation versus 199 patients with acute PE who received anticoagulation alone. There was no difference in recurrent PE rate at 3 or 6 months and so the conclusion was that there was no added benefit of adding such retrievable filters when anticoagulation was feasible.⁷⁵

Only 11 of the 108 patients with massive PE in the ICOPER registry received an IVC filter but none of the patients with filters developed recurrent PE, and 10 of 11 survived at least 90 days.³ Although a very small sample size, these findings suggest that IVC filter placement may be reasonable in PE patients with poor cardiopulmonary reserve. The only ironclad indications for IVC filter placement are in PE patients with contraindications to anticoagulation or with active bleeding. It is also reasonable to place an IVC filter if recurrent VTE occurs on adequate anticoagulation.⁴³

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Fiberoptic Bronchoscopy

Lillian L. Emlet

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INTRODUCTION

Fiberoptic bronchoscopy is a useful skill for the emergency physician. This procedure allows navigation of the upper airways, placement of endotracheal tubes, and evaluation of the proximal and distal airways. As an extension of airway and ventilator management, proficiency in flexible fiberoptics is an important tool used in critical care medicine.

The history of the bronchoscope began in 1897 with Gustav Killian, affectionately known as the “father of bronchoscopy” when he used direct visualization of trachea/bronchi to remove a foreign body (bone lodged in R main). In the 1900s, rigid bronchoscopy improved treatments for lung cancer, and in 1904 Chevalier Jackson added an electric light source and suctioning capability. By 1966, Dr. Shigeto Ikeda (Pentax) created the first flexible fiberoptic bronchoscope, and use expanded from evaluation intraoperatively to guide pulmonary sample collection and surgical biopsies. In the 1980s, Asahi Pentax replaced fiberoptic bundles with a charge coupled sensor at the tip of the scope to allow video screen projection of images. Now multiple manufacturers have fiberoptic devices of varying sizes, lengths, and calibers, with even small portable endoscopes for procedural guidance. With the advent of video laryngoscopy, similar technology now has extended to bronchoscopes, creating video bronchoscopes that are less prone to breakage.

The purpose of this chapter is to review the knowledge required to perform bronchoscopy safely for a wide variety of common reasons in the intensive care unit (ICU) and emergency department (ED). Considerations for performing bronchoscopy in the ED usually relate to placement of airway (procedural guidance for endotracheal tube) or treatment of

large airway occlusion (removal of large mucus plug). Reasons for the procedure to be performed in the ED include urgent need to establish airway (clinical decompensation, stridor, upper airway occlusion) or hypoxia.

Optical fibers within the bronchoscope are polymers that guide light and use video to display images. A channel providing ability to deliver medications such as lidocaine, suctioning of secretions or hemorrhage, and delivery of tools for snaring foreign bodies is standard for bronchoscopes. Luminal size determines strength and ability to effectively clear secretions; “pediatric” scopes, often measuring 4–5 mm in diameter, are less effective for hemoptysis, and are usually reserved only for procedural guidance of challenging upper airway anatomy.

Overall, bronchoscopy is a safe procedure with a mortality of 0% to 1%. There is a complications rate of 0.08% to 10% (PTX). Minor complications include infection, bleeding, hypoxemia, cardiac arrhythmia (secondary to lidocaine toxicity), and medication reaction (anesthesia or sedatives).^{1,2} Other complications include tachycardia/bradycardia, bronchospasm/laryngospasm, cough, dyspnea, sore throat, apnea, seizure, desaturation, pneumothorax, and pulmonary edema. Hypoxemia is common during this procedure due to sedation impairing ventilation, and lavage of alveolar segments^{3–5} (Tables 14-1 and 14-2).

PREPARATION

Preparation for bronchoscopy requires thought and consideration for preparing the patient (verbal consent and explanation, sedation and analgesia, positioning) and preparing equipment (vacuum suction source, sterile culture or brush collection traps, suction tubing, lubricant, slip tip syringes,

 **TABLE 14-1: Diagnostic & Therapeutic Indications**

Diagnostic & Therapeutic Indications
Guidance of endotracheal intubation
Pulmonary toileting (mucus plugging, removal of sputum)
Detection & staging of lung CA (transbronchial biopsy of lymph nodes, biopsy of endobronchial lesions)
Evaluation of diffuse lung diseases (sarcoid, interstitial pneumonias, inhalational burn injury)
Evaluation & treatment of hemoptysis
Evaluation of traumatic injury
Evaluation of surgical anastomoses (lung transplant) or
Evaluation of subglottic and tracheal stenosis (with stent placement/balloon angioplasty)
Evaluation and treatment of hemoptysis (guidance of balloon tamponade with bronchial blockers, guidance of vasoconstrictor or thrombin injection)
Evaluation of lung transplant allograft function (biopsy, culture specimens)
Obtaining culture specimens for bacterial, viral pneumonias (BAL or PSB)
Placement and confirmation of endotracheal tubes (for anticipated difficult intubations when oxygenation can be maintained)
Restricted neck extension (unstable cervical spine fractures, rheumatoid arthritis)
Morbid obesity
Supraglottic anatomy distortion (tumor, angioedema)
Removal of airway foreign bodies
Specialized procedures (laser therapy, brachytherapy, cryotherapy, stent placement)
Removal of mucus plugs not relieved by chest physiotherapy techniques

 **TABLE 14-2: Contraindication and Side Effects**

Relative Contraindications
Inadequate oxygenation (elevated PEEP, excessive FiO ₂ 100%)
Inadequate ventilation (inability to tolerate decreased V _e)
Cardiovascular instability, ischemia, dysrhythmias ⁶
Increased ICP ⁷
Coagulopathy (INR > 1.5, plts < 20)
Inadequate size ETT (< 7.5 mm diameter)
Pregnancy
Uncooperative patient
Absolute Contraindications
Inability to maintain oxygenation
Major airway bleeding
Absence of consent
Inadequate facilities
Inadequate ventilation
Side effects
Bronchospasm
Inability to ventilate
Hemorrhage
Trauma (immunosuppression, malnutrition, debility, age)

sterile saline irrigation). The bronchoscope and video connections should be tested prior to initiating the procedure to ensure working channels, light source, scope flexion function, and adequacy of image acquisition.

Patient preparation is key to success for this procedure, as patients can be awake and lightly consciously sedated throughout this procedure, and communication throughout the procedure is necessary. Patient expectations and a detailed explanation of the process of topical anesthesia administration and expectations of remembering coughing during procedure are important. Assessment of adequate topical anesthesia or nares or oropharynx should be done prior to performing bronchoscopy, with expectation of further “spray as you go” topicalization of vocal cords and carina.

Medications for light to moderate sedation include propofol, benzodiazepines, Precedex, ketamine, and opioids.^{8,9} Choice of sedation requires assessment of cardiac and respiratory risk, including known coronary ischemia or insufficiency, and hypoxemia or hypoventilation. Optimizing hypoxemia with a high-flow nasal cannula is an option to improve status before bronchoscopy, as well as mild sedation with low-dose ketamine, Versed, and fentanyl.

The “spray as you go” technique of topical anesthesia requires lidocaine administration in small aliquots to key areas that initiate cough: the posterior pharyngeal wall, vocal cords, and carina.¹² Maximum dose is 4 to 5 mg/kg actual body weight with usual concentrations of 1% to 2% lidocaine. Lidocaine is rapidly absorbed via oral mucosa and an effective topical anesthetic. Symptoms of lidocaine toxicity (onset 30 sec to 60 min) include CNS, cardiovascular, hematologic and allergic: exhibited by perioral numbness, metallic taste, lightheadedness, dizziness, disorientation, drowsiness, chest pain, palpitations, shortness of breath, diaphoresis, rash, and urticaria. Severe symptoms of lidocaine toxicity include: muscle twitching, convulsions, unconsciousness/coma, hypotension, syncope, respiratory/cardiovascular depression, and methemoglobinemia.

Cetacaine (benzocaine) can also be used for oropharyngeal anesthesia, with methemoglobinemia being the greatest risk of this medication’s side effect profile. Methemoglobinemia has been most commonly described with benzocaine, but lidocaine and prilocaine have also been implicated. Symptoms begin when 10% to 40% levels of methemoglobin occur, exhibited by cyanosis (refractory hypoxemia), tachypnea, dyspnea, dizziness, and syncope. The antidote for methemoglobinemia is methylene blue (1 mg/kg).

For situations in which hemoptysis is indication for bronchoscopy, first-line treatment is topical vasoconstrictors. Lidocaine with epinephrine (1:1,000) is used to treat initial bleeding episodes, with epinephrine causing vasoconstriction of tracheal mucosa. Epinephrine reduces the systemic absorption of lidocaine.

Adjuncts used in bronchoscopy include medications for cough suppression and anti-sialogogues. The most common of these in adult populations, glycopyrrolate (0.005 mg/kg) or atropine (0.1 mg/kg) are options for pretreatment; however, these are usually not necessary due to lack of noticeable difference in patient or physician benefits.¹⁰

Paralytics are often used in situations in which bronchoscopic side effects are undesirable (e.g., increased intracranial pressure in traumatic brain injury). Vecuronium or cisatracurium (liver/kidney dysfunction) for intracranial pressure (ICP) is commonly used. For cardiovascular protection, clonidine IV/PO 300 mcg has been described to blunt the response.¹¹

Preoxygenation of the patient can be achieved with a 100% NRB mask with a hole cut out of the side of the mask to facilitate placement of the bronchoscope, or a high-flow nasal cannula oxygen (e.g., 80% at 40 L/min) can be used.^{13,14} If patients are on mechanical ventilation, ventilator settings should be adjusted to 100% FiO₂, mandatory A/C ventilation, and consider adjusting high-pressure limits/alarms, decreasing tidal volume (TV), increasing respiratory rate, decreasing flow rates/lengthening I time, or removal from ventilator and performing bag valve mask (BVM) ventilation manually.

Due to differing sizes of endotracheal tubes and differing sizes of fiberoptic bronchoscopes, ventilation during

bronchoscopy can be very limited, and air trapping from bronchoscopic obstruction during exhalation causes the most common complication to be pneumothorax. This can be prevented with attention to length of time the bronchoscope is in the endotracheal tube, as desaturation can be a late finding.

PROCEDURAL CONSIDERATIONS

There is some limited evidence that including a protected specimen brush (PSB) increases specificity of culture.¹⁵ However, most bronchoalveolar lavages (BAL) are adequate for diagnosis of pneumonia. Instillation of 100–300 mL of sterile saline is commonly used, in aliquots of 20–100 mL, with returned volume into specimen trap usually only 50% of instilled volume. Specimens need to be at least 20–40 mL, and additional aliquots are needed for viral or atypical pathogens. Instillation of lavage fluid will decrease arterial oxygenation (Figure 14-1).¹⁶

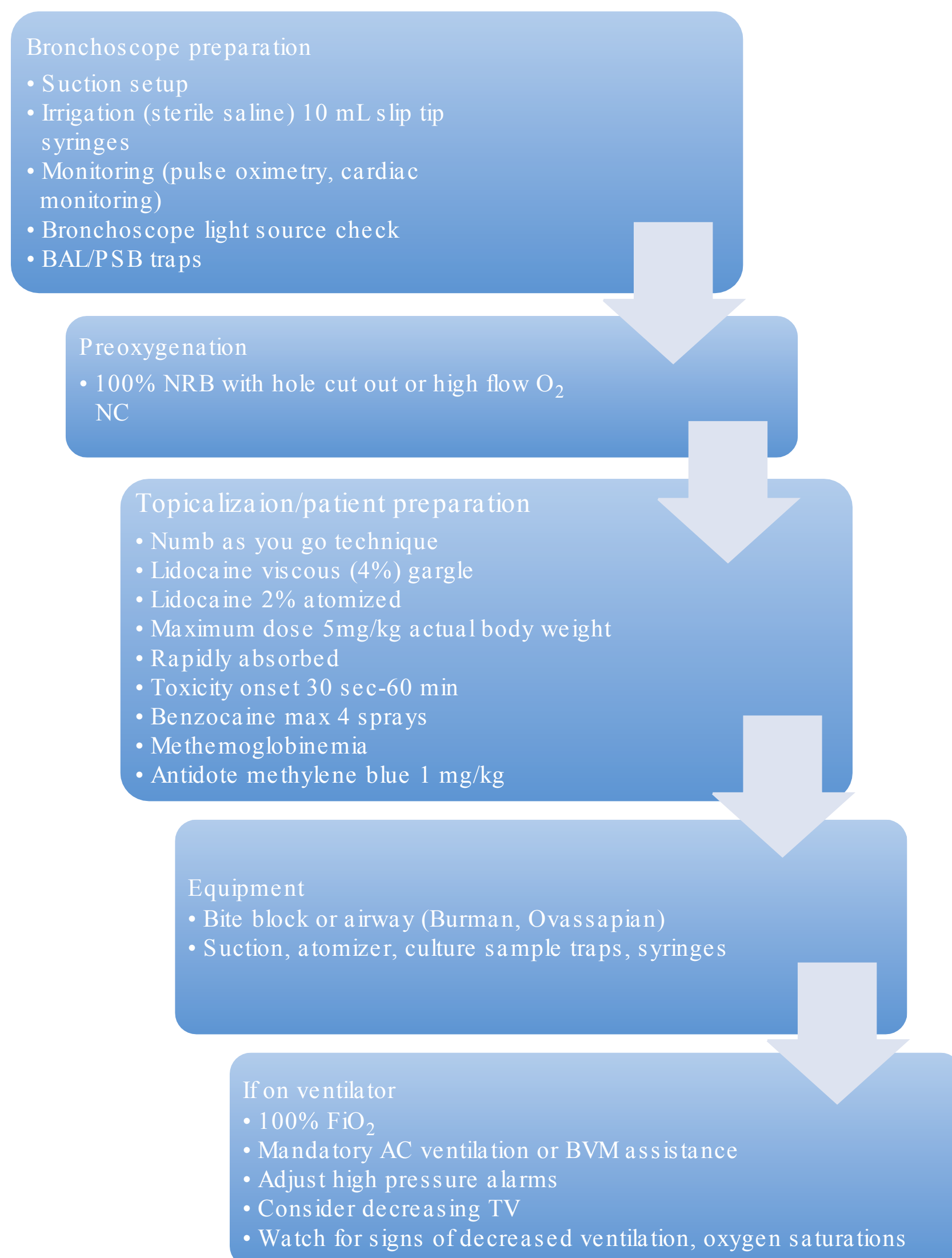


FIGURE 14-1 How to obtain a bronchoalveolar lavages (BAL).

For most fiberoptic intubation, the nares or mouth can be used to place the endotracheal tube, with choice dependent upon indications and contraindications (e.g., angioedema vs. restricted mouth opening or spine mobility vs. coagulopathy). Counterclockwise rotation of the ETT during advancement over the bronchoscope at 14–16 cm (laryngeal inlet) helps beveled tip pass through the vocal cords, which is the most common site of difficulty. Excessive force should not be used in order to prevent cord trauma or tracheal injury. Communicating continuously with the semi-awake patient is necessary in order to facilitate cooperation and comfort. Figure 14-2 shows mucus being aspirated.

Obtaining Cultures via BAL or PSB:

BAL (better if no obvious pus, do not send thick secretions or mucus plug)

1. Clear airways of large mucus plugs if applicable
2. Advance bronchoscope to bronchial segment of concern and wedge

3. Irrigate with 20 mL aliquots of sterile saline while wedged (can repeat \times 4)
4. Watch irrigant solution go in, suction immediately once finished & watch wash solution exit
5. Slight in/out motion of bronchoscope may be necessary due to collapse of airway during suctioning while wedged
6. Excessive over-vigorous application of suction will cause airway collapse and decrease return, try to use gentle constant suction and in a pulsatile fashion

PSB (better tolerated if severe hypoxemia)

1. Advance bronchoscope to bronchial segment of concern
 2. Advance PSB catheter out of scope
 3. Eject the distal carbon wax plug
 4. Advance brush into sub-segment and rotate brush within secretions
 5. Retract brush into catheter sleeve
 6. Remove entire catheter from bronchoscope
 7. Wipe distal portion of catheter with 70% alcohol swab
 8. Advance forward the brush portion
 9. Cut brush with sterile scissors into 1 mL of sterile saline
-

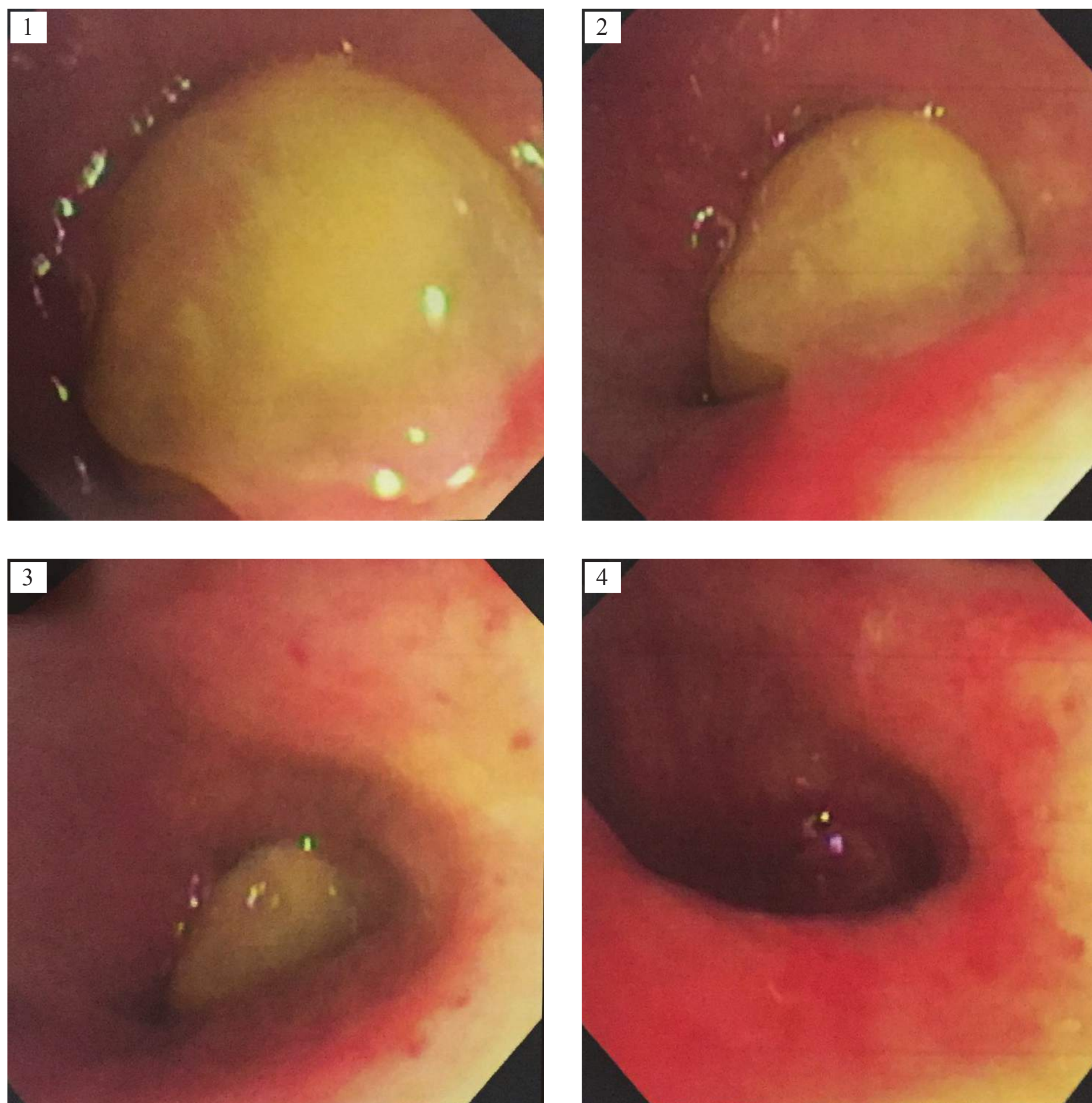


FIGURE 14-2 Example of a BAL; Photos 1, 2, and 3 reveal mucus being suctioned out, Photo 4 shows mucus cleared.

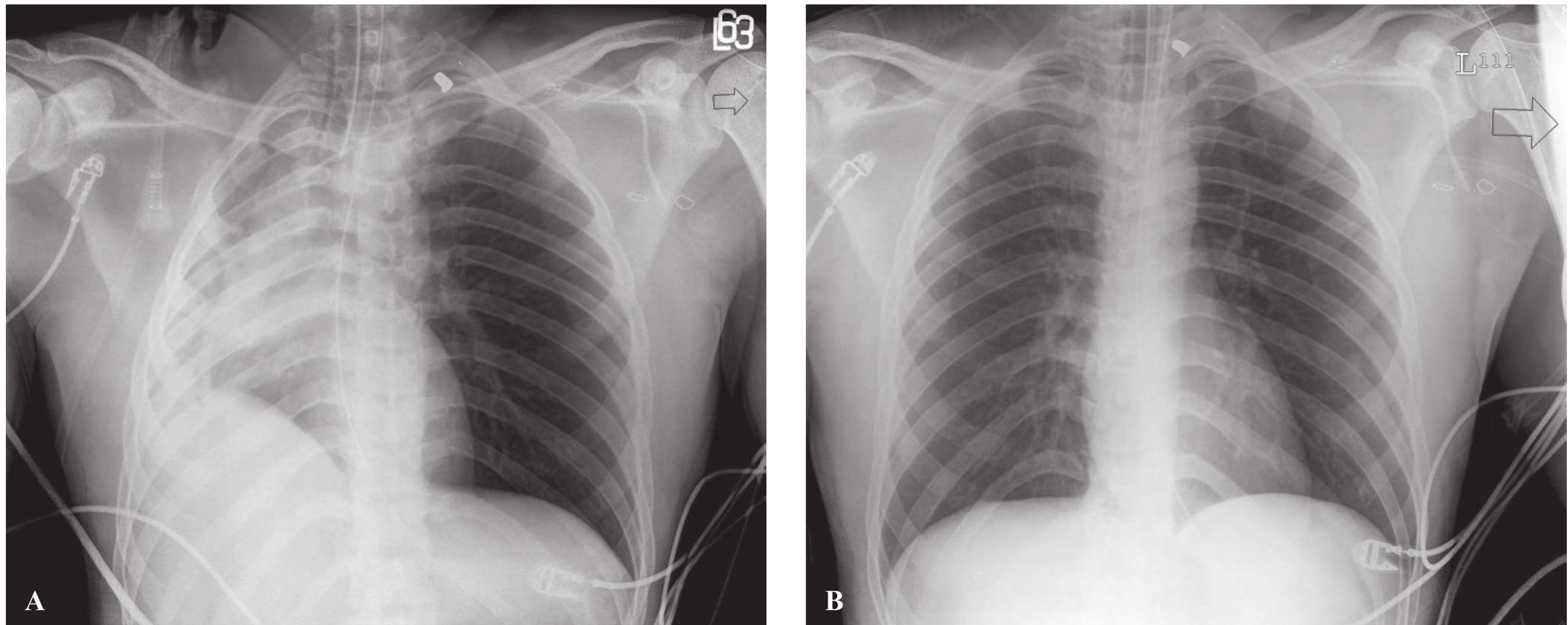


FIGURE 14-3 **A.** Right middle lobe opacification, suspicious of a mucus plug. **B.** Post-bronchoscopy and reopening of the lobe.

PROCEDURAL MONITORING

Patients should be monitored to ensure adequate oxygenation, hemodynamics, and ventilation if possible. Continuous pulse-oximetry, ECG monitoring, blood pressure, and sedation/paralysis assessments, and consideration for continuous end-tidal CO₂ monitoring of ventilation should be employed.

POST-PROCEDURAL PROCEDURES

Consider post-bronchoscopy chest x-ray (CXR) to assess improvement or change in atelectatic lung; however, this is not required. See an example of drastic changes postprocedure in Figure 14-3A,B. Usual recruitment continues to occur on mechanical ventilation. Thus, consideration of leaving on a slightly higher PEEP for a few hours may assist in prevention of atelectasis following bronchoscopy, especially if BAL has been performed, as the most common cause of hypoxia transiently after bronchoscopy is the lavaged fluid needing to be reabsorbed. CXR often shows interstitial changes that usually resolve in 24 hours.

Cleaning the bronchoscope is critical to prevention of transmission of nosocomial infections between patients. Similar to other endoscopes, immediate large debris cleaning is necessary with mechanical brushes and enzymatic cleaners. Strict protocol adherence by respiratory therapy and sterilization staff should be maintained and quality checked, and consideration of protocols and checklists to ensure all the correct steps are performed even in the cleaning and sterilization process.

Sedation recovery of the patient requires monitoring of hemodynamic, respiratory, and neurologic status by trained nursing staff until normal parameters are achieved. If reversal agents (naloxone, flumazenil) need to be administered, the observation recovery time should be extended. Monitoring should continue until the patient has normalized neurologic and vital signs and reassessment of pharyngeal anesthesia (gag) should be assessed before oral intake can be cleared.

SPECIAL SITUATIONS

Common additional uses of the bronchoscope include for guidance and confirmation of double lumen tube placement during thoracic surgery, emergent control of hemoptysis, and asymmetric ARDS. Interventional procedures performed by pulmonologists include virtual and ultrasound-guided bronchoscopic procedures (e.g., dilation of tracheal stenosis and stent placement, endobronchial ultrasound transbronchial needle aspiration (EBUS TBNA), including thermoplasty for refractory asthma treatment, nonsurgical lung resection (placement of intrabronchial valves) and endobronchial lymph node biopsy.

SUMMARY

Bronchoscopy is a useful procedure for upper airway obstructions to guide endotracheal tube placement, clearance of obstructing secretions, removal of foreign material, and obtaining culture specimens. With practice, preparation and protocols, bronchoscopy is a safe procedure for pulmonary toileting, assessment of hemoptysis, and guidance of airway procedures.

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CARDIO VASCULAR DISORDERS

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Hemodynamic and Perfusion Monitoring

Elizabeth Lea Walters • Vi Am Dinh • H. Bryant Nguyen

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INTRODUCTION

Critically ill patients are frequently encountered in the emergency department (ED) and intensive care unit (ICU), such that practitioners in both locations are required to quickly identify and resuscitate unstable patients. Additionally, with the problems of hospital overcrowding and subsequent boarding of critical patients in the ED, hemodynamic management after the initial resuscitation is prudent and mandatory in the ED.

Hemodynamic monitoring is an integral part of the management of critically ill patients, having a diagnostic, therapeutic, and resuscitation role. The analysis of hemodynamic variables beyond traditional vital signs allows the clinician to differentiate various causes of hemodynamic instability and intervene appropriately. This chapter will discuss hemodynamic monitoring methods.

ARTERIAL BLOOD PRESSURE MONITORING

Arterial blood pressure is a measure of the force exerted by circulating blood through a blood vessel. It is regulated via changes in the α -adrenergic tone of afferent vessels and varies in the different organs. For example, cerebral and coronary vessels have few α -adrenergic receptors, thus tissue perfusion depends directly on perfusion pressure in these vessel beds. However, tissue perfusion pressure cannot be measured directly, and arterial blood pressure has been used as a surrogate.¹

Cardiac output (CO) and vascular tone are controlled via autoregulation, and hypotension reflects a failure of these

mechanisms. Hypotension can result from severe cardiogenic or hemorrhagic shock (decreased CO) despite preserved vasomotor tone, or from a primary loss of vasomotor tone independent of CO, as in spinal cord trauma and septic shock. Normal blood pressure does not equate with cardiovascular stability, since it can occur in the setting of circulatory shock if systemic vasomotor tone proportionally increases. As a result, hypotension is always pathologic and reflects a failure of normal circulatory homeostatic mechanisms.

Autoregulation is determined by mean arterial pressure (MAP), and the normal range for most tissues is 65 to 120 mm Hg, keeping in mind that the contributors to MAP are CO and systemic vascular resistance ($MAP = CO \times SVR$). As MAP decreases below 60 mm Hg, organ perfusion pressure is compromised and, if sustained, results in organ failure and death.² Thus, one target of hemodynamic monitoring is to keep the MAP higher than 65 mm Hg. However, the optimal MAP varies according to the underlying cause of hemodynamic instability. For example, in septic shock, increasing MAP greater than 65 mm Hg with fluids and vasopressors increases oxygen delivery, but does not improve indices of organ perfusion or 28- and 90-day mortality.^{3,45} In fact, use of vasopressors to increase MAP higher than 65 mm Hg may actually result in increased mortality.⁶ In post-cardiac arrest patients, ACC/AHA guidelines recommend a systolic blood pressure (SBP) of greater than 90 mm Hg and MAP greater than or equal to 65 mm Hg.^{7,8} In traumatic brain injury, observational studies suggested that an SBP less than 90 mm Hg was an independent predictor for increased morbidity and mortality.⁹

Trauma patients with shock from uncontrolled bleeding, but no severe head injury, can tolerate a lower MAP. Studies demonstrated that delayed fluid resuscitation until definitive surgical intervention has been shown to improve survival.¹⁰ The International Task Force on Shock and Hemodynamic Monitoring recommended initially targeting a MAP of > 65 for non-trauma patients, although patients with septic shock and history of hypertension, or those who show clinical improvement with higher MAPs, may benefit from a higher target.¹¹

SBP represents maximum pressure during ventricular ejection, diastolic pressure is the lowest pressure in the blood vessels between heartbeats during ventricular filling, and pulse pressure is the difference between the two. Both SBP and diastolic pressure vary significantly throughout the vascular system. Thus, SBP can increase by up to 20 mm Hg, while the diastolic pressure similarly decreases as the pressure wave moves from the aorta to the periphery. However, MAP varies by only 1 to 2 mm Hg throughout the arterial system.¹² MAP can be estimated as the sum of the diastolic pressure and one third of the pulse pressure.¹³

Noninvasive Measurement

PALPATION

SBP can be estimated by palpation of the radial, femoral, or carotid pulse in an emergency situation, to reflect a minimum SBP of 80, 70, or 60 mm Hg, respectively. However, this method overestimates SBP when compared with invasive measurements in patients with hypovolemic shock.¹⁴

SPHYGMOMANOMETRY

The most common method of determining arterial blood pressure is through the use of sphygmomanometry. With sphygmomanometry, blood pressure can be measured using auscultation of Korotkoff sounds or via automated oscillometric devices.¹³ With oscillometric devices, the point of maximal oscillation corresponds to MAP. SBP and diastolic pressure are estimated by an empiric algorithm.¹⁵ Oscillometric devices, in general, are more accurate than auscultation, although they may underestimate systolic blood pressure by as much as 19% and overestimate diastolic blood pressure up to 27%.¹⁶ Variability in the auscultatory method can be due to improper cuff size, cuff placement, placement of the stethoscope bell, cuff deflation rate, dysrhythmia, observer bias, and faulty equipment.¹⁷ Complications related to prolonged use of an automatic oscillometric device are rare, but include potential skin and nerve damage.^{18–20} Other noninvasive devices for continuous arterial pressure measurements have been shown to be feasible for use in the ED, but may not be accurate during hypotension.^{21,22}

Invasive Measurement

Korotkoff sounds and pressure oscillations are diminished in patients with marked vasoconstriction and can underestimate SBP by more than 30 mm Hg when compared with direct

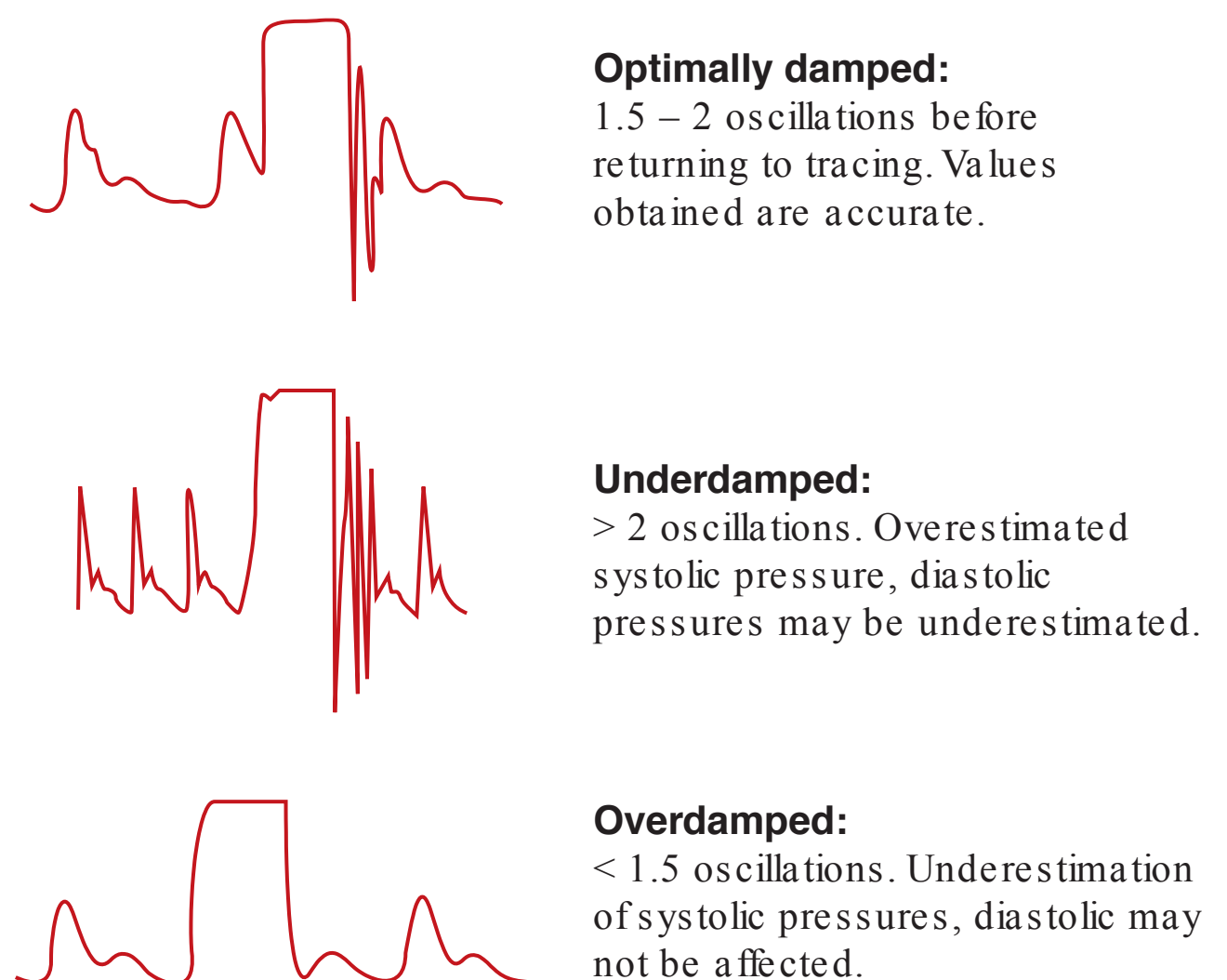


FIGURE 15-1 Square wave flush test. A bolus flush of the catheter results in a square wave tracing. The number of oscillations before returning to the blood pressure tracing indicates proper damping.

measurements.²³ Invasive monitoring via intra-arterial catheterization provides instantaneous measures of MAP and is the preferred method in critical ill patients.

The radial artery is the most frequent site for arterial catheterization, although the femoral artery may be appropriate in emergent situations and hypotensive patients.²⁴ Except in states of severe peripheral vasoconstriction, in which radial measurements may underestimate central pressure,¹² radial and femoral artery measurements are interchangeable.²⁵ Other potential sites including axillary, brachial, dorsalis pedis, ulnar, tibial posterioris, and temporal arteries are rarely used. Complications from intra-arterial catheterization include infection, bleeding, vessel occlusion, and fistula formation.^{26,27}

After successful arterial catheterization, connection of the catheter to the pressure transducer should reveal an arterial waveform. The square wave flush test is applied to determine if an artifact in the tubing and recording system is damping the pressure measurements (Figure 15-1). The most common source of error is due to air bubbles in the tubing system.¹² An overdamped system suggests trapped air bubbles in the tubing, resulting in falsely lowered pressure measurements, while an underdamped system will result in excessive resonance and overestimation of SBP and underestimation of diastolic pressure. Further flushing of the system to remove the air bubbles or replacement of the tubing may be required. Indications for arterial catheterization are illustrated in Table 15-1.

MONITORING CENTRAL VENOUS PRESSURE

Intravenous fluids are a mainstay in the resuscitation of critical patients and are used to increase CO and arterial pressure to improve tissue oxygenation. In fact, 50% of critically ill patients will have improvement in CO when given a fluid challenge.²


TABLE 15-1: Indications for Placement of an Arterial Catheter

- Continuous blood pressure monitoring of hemodynamically unstable patients
- Monitoring for optimal MAP during administration of vasoactive drugs
- Frequent blood draws for blood gases and other laboratory studies
- Calculation of pulse pressure variation (PPV) and cardiac output (CO) via pulse contour analysis

Central venous pressure (CVP) is the pressure in the great thoracic veins proximal to the right atrium. It is measured at end-expiration and is determined relative to atmospheric pressure. Using this definition, CVP may not be an accurate representation of intravascular volume as it can be affected by both anatomic and physiologic factors, such as tricuspid valve disease, cardiac compliance, abnormal right ventricular function, pulmonary vasculature disease, and arrhythmias. Other factors can also affect its measurement (Table 15-2). Thus, CVP in and of itself does not reflect blood volume status.^{28,29} While CVP monitoring is generally useful to assess global volume status, it is less useful as a guide to resuscitation as it is only a reflection of pressure in the right atrium. Instead, the relationship between CO and intravascular volume change is depicted by the Starling curve. Unfortunately, a static measurement of CVP does not show where along that curve an individual patient's measurements are located. However, most clinicians accept that a low CVP indicates hypovolemia, while an elevated measurement suggests volume overload, with normal


TABLE 15-2: Factors Affecting Central Venous Pressure

Central venous blood volume	Venous return
	Cardiac output
	Total blood volume
	Regional vascular tone
	Vascular tone
Cardiovascular compliance	Compliance of right ventricle
	Myocardial disease
	Pericardial disease
	Cardiac tamponade
	Changes with respiration
Intrathoracic pressure	Positive end-expiratory pressure (PEEP)
	Intermittent positive pressure ventilation
	Tension pneumothorax
Tricuspid valve disease	Stenosis
	Regurgitation
	Junctional rhythm
Dysrhythmia	Atrial fibrillation
	Atrioventricular dissociation
Transducer reference level	Position of patient

Adapted with permission from Polanco PM, Pinsky MR. Practical issues of hemodynamic monitoring at the bedside, *Surg Clin North Am.* 2006 Dec;86(6):1431–1456.

ranges from 0 to 10 mm Hg.³⁰ When used in this manner, the astute clinician must consider possible contributing factors that may lead to a false estimation of volume status.

Although studies have shown that measures of CVP do not necessarily correlate with circulating blood volume and even changes in CVP may not correlate with changes in blood volume, a CVP lower than 4 mm Hg in the critically ill patient should prompt fluid resuscitation with careful monitoring.^{11,29} The “5–2 rule” by Weil et al. to estimate a patient's volume status may be performed rapidly in the ED.³¹ An initial CVP measurement is obtained, and then a 10 to 20 mL/min bolus of normal saline is infused for 10 to 15 minutes (e.g., 250 mL over 15 minutes). An increase in CVP > 5 mm Hg would indicate volume overload. However, if CVP increases 2 mm Hg or less, hypovolemia should be suspected and a second fluid bolus given. Incorporated in a therapeutic protocol, CVP of 8 to 12 mm Hg during resuscitation of the critically ill patient in the ED is a reasonable target.³²

Noninvasive Measurement of CVP

JUGULAR VENOUS PULSATION

When invasive measurement of CVP is not feasible, internal jugular venous pulsation (JVP) may be used to estimate right atrial pressure.³³ The sternal angle is approximately 5 cm above the center of the right atrium regardless of the patient's position. To obtain JVP, position the patient at a 45° angle. The vertical distance between the jugular pulsation and the sternal angle is added to 5 cm to estimate CVP in cm H₂O. The upper limit of normal for the internal jugular vein (IJV) to pulsate is approximately 4.5 cm vertically above the sternal angle (or 9.5 cm H₂O total). Any pulsation above 4.5 cm at 45° indicates an elevated CVP. Visualization of the IJV pulsation by physical examination is not always possible in the ED, especially in trauma, obese, or uncooperative patients.

ULTRASONOGRAPHY

Ultrasound can be used to determine elevated jugular venous pressure in the ED. The right IJV is viewed with a high-frequency linear transducer (7–9 MHz) in the transverse plane with the patient in a semi-upright position. CVP is greater than 10 cm H₂O if it appears distended and larger than the adjacent common carotid artery. A near-complete collapsed IJV in the transverse view in the supine position indicates a very low CVP. In one recent study, measurement of the IJV with ultrasound showed that a mean diameter in patients with CVP less than 10 cm H₂O was 7.0 mm versus 12.5 mm in patients with CVP of 10 cm H₂O and greater. Measurement of end-expiratory diameter in supine patients exhibited a high correlation to invasive measures of CVP.³⁴

Another method is to visualize the right internal jugular in the longitudinal plane. With the patient in a semi-upright position, the location at which the vein tapers (collapses) is the site of the JVP (Figure 15-2). The vertical distance in centimeters between this point of vein collapse and the sternal angle is measured, and added to 5 cm, giving JVP in cm H₂O.³⁵

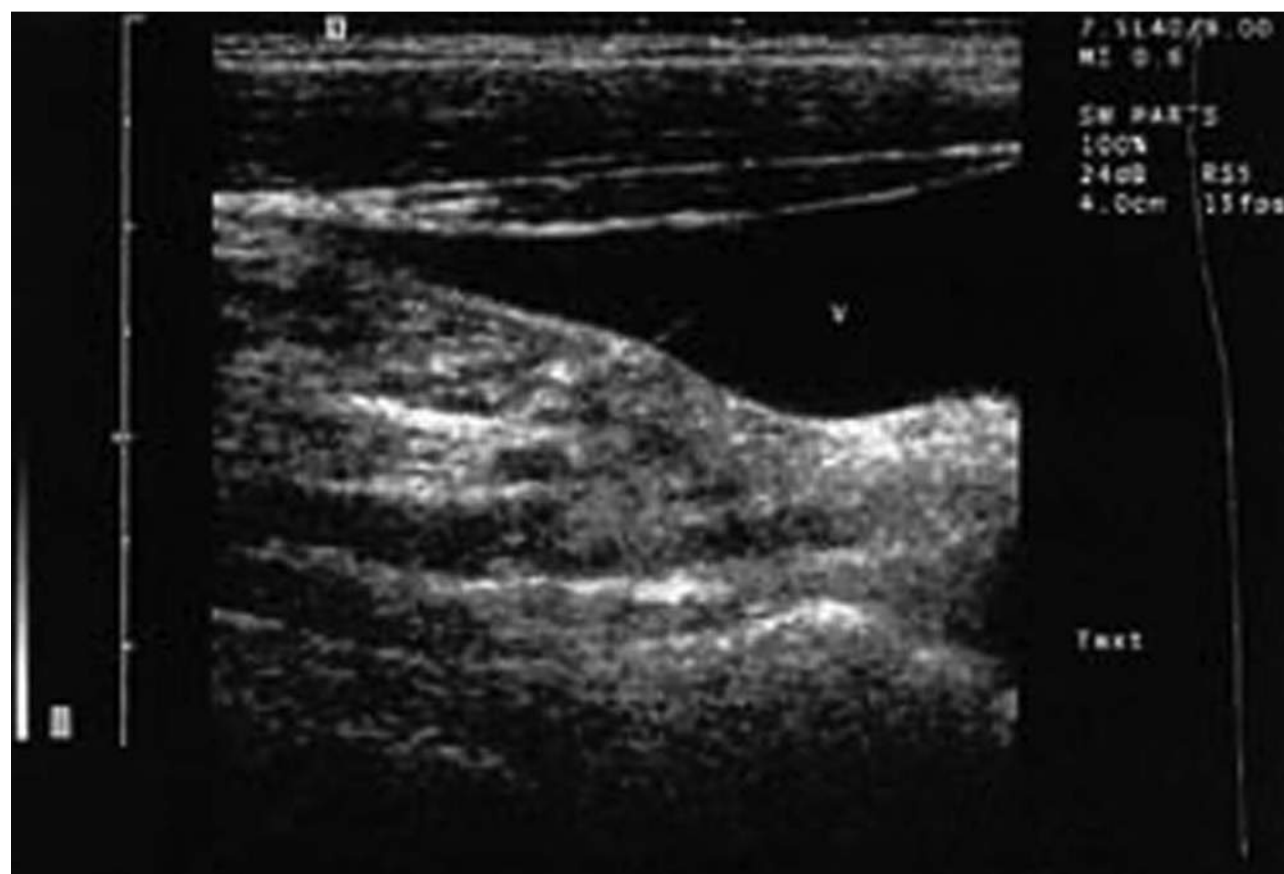


FIGURE 15-2 Estimating jugular venous pressure. An ultrasound longitudinal view of the internal jugular vein shows tapering at the point of jugular venous pulsation. (Reproduced with permission from Lipton B. Estimation of central venous pressure by ultrasound of the internal jugular vein. *Am J Emerg Med.* 2000 Jul;18(4):432–434.)

Inferior vena cava (IVC) assessment can be used to estimate right atrial pressure (RAP) and fluid responsiveness. The technique involves placing a phased array or curvilinear ultrasound transducer on the epigastrium of the patient in long axis and identifying the IVC as it enters the right atrium. IVC measurements are performed 2 cm distal to the hepatic vein (Figure 15-3).³⁶ A maximal IVC diameter < 2 cm correlates with a CVP < 10 mmHg. For spontaneously breathing patients, an IVC with greater than 50% collapsibility (maximum IVC diameter - minimum IVC diameter)/maximum IVC diameter indicates right atrial

pressure is < 8 cm H₂O. For mechanically ventilated patients, the IVC distensibility index can predict fluid responsiveness. An IVC distensibility index greater than 18% [(max-min)/min] or 12% [(max-min)/mean] corresponds to fluid responsiveness,^{37,38} whereas maximal IVC diameter appears to more accurately estimate overall CVP.³⁹

Invasive Measurement of CVP

Traditionally, CVP is monitored by placing a fluid-filled catheter into the internal jugular or subclavian vein with the tip in the distal superior vena cava. The transducer should be placed at the level of the right atrium, or approximately 5 cm below the sternal angle. Because CVP measurement is affected by respirations, measurement should be taken at the end of expiration when pleural pressure has minimal effect and CVP closely approximates cardiac transmural pressure. An acceptable CVP waveform is shown in Figure 15-4. The c-wave represents bulging of the tricuspid valve into the right atrium and occurs at the onset of systole. The base of the c-wave is used to determine a CVP value because it is the final pressure in the ventricle before the onset of contraction, reflecting *preload*.³⁰

Occasionally, in patients with coagulopathy, patients in whom subclavian and/or IJV catheterization was unsuccessful or resulted in a complication, or those requiring immediate access, femoral vein catheterization is required to measure CVP. Studies have shown that femoral CVP may be reliable, although use of this site is often discouraged due to increased risk of infection and hematoma formation.⁴⁰ Other studies have shown that changes in venous pressure measured from a peripheral vein may correlate with similar changes in CVP.⁴¹

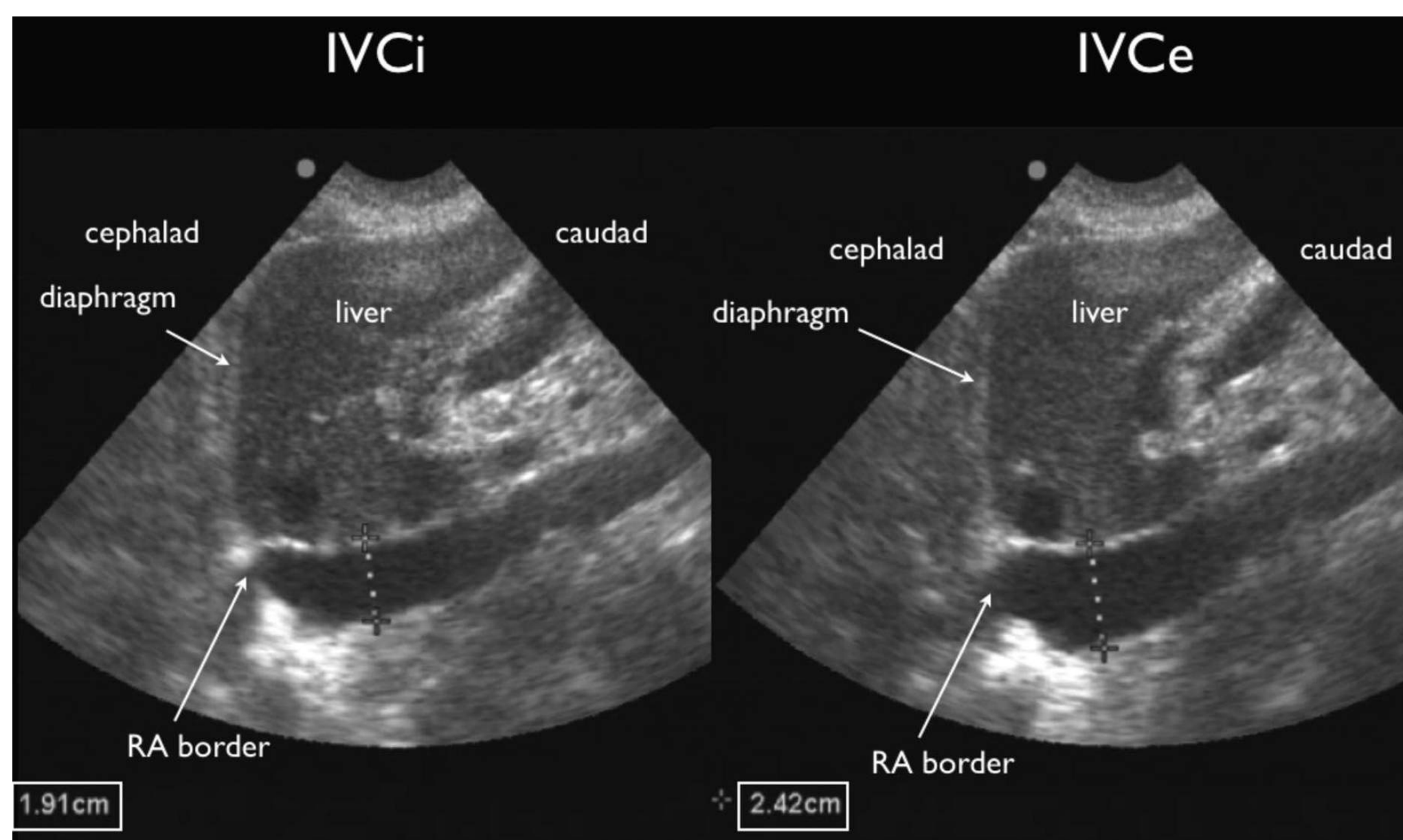


FIGURE 15-3 Ultrasonographic determination of inspiratory inferior vena cava (IVCi) and expiratory inferior vena cava (IVCe) in a spontaneously breathing patient. (Reproduced with permission from Nagdev AD, Merchant RC, Tirado-Gonzalez A, et al: Emergency department bedside ultrasonographic measurement of the caval index for noninvasive determination of low central venous pressure, *Ann Emerg Med.* 2010 Mar;55(3):290–295.)

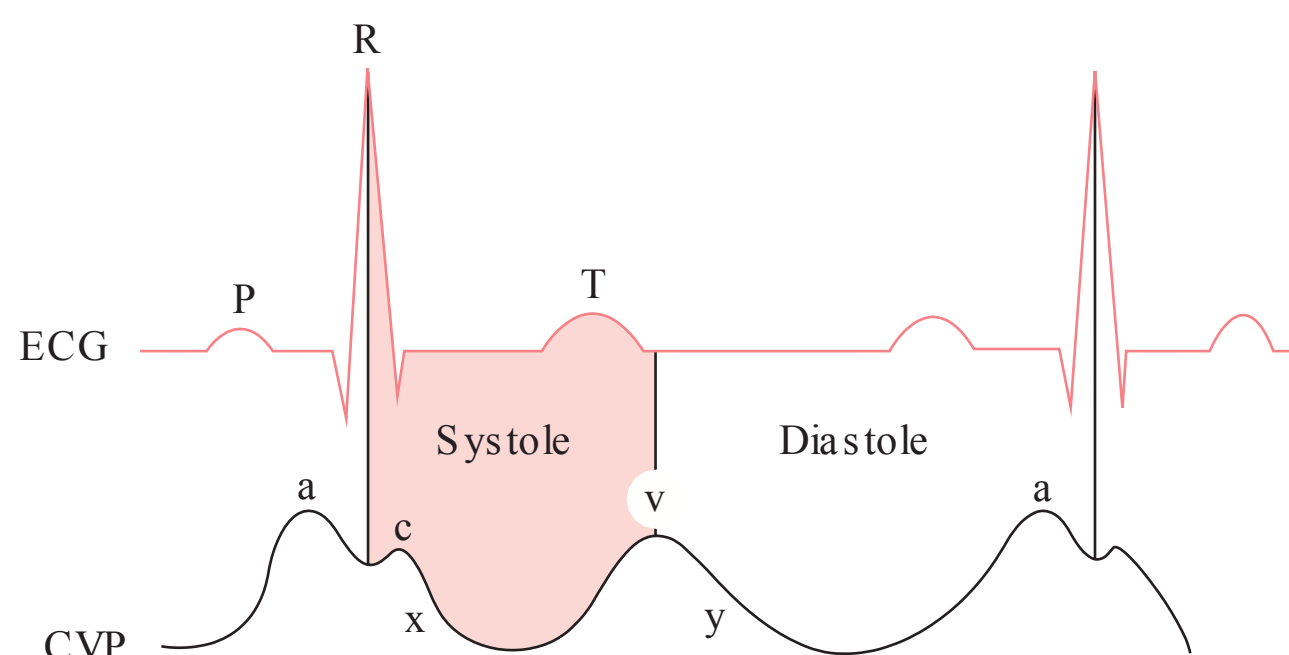


FIGURE 15-4 Central venous pressure waveform. Comparing the central venous waveform with the electrocardiogram waveform: (*a-wave*) atrial contraction, (*c-wave*) bulging of tricuspid valve into the right atrium at onset of systole, (*x-descent*) atrial relaxation, (*v-wave*) increase in atrial pressure due to venous return during systole, before the tricuspid valve opens, and (*y-descent*) atrial emptying into the ventricles during diastole.

Complications associated with placement of central venous lines are listed in Table 15-3. Other indications for central venous catheterization include fluid and vasopressor administration, unsuccessful or inadequate peripheral venous access, central venous oxygenation (ScvO₂) measurement, pulmonary artery catheterization, and transvenous pacemaker placement.

CARDIAC OUTPUT MONITORING

The primary goal of resuscitation from shock is to reverse tissue hypoperfusion. Oxygen delivery is reliant on CO and the delivery of oxygenated arterial blood to the tissues. CO is in turn affected by the interaction of preload, contractility, and afterload. Vital signs and physical exam are not sufficient



TABLE 15-3: Complications of Central Venous Lines

	Internal Jugular Vein (%)	Subclavian Vein (%)	Femoral Vein (%)
Arterial puncture	6.3–9.4	3.1–4.9	9.0–15.0
Hematoma	< 0.1–2.2	1.2–2.1	3.8–4.4
Pneumothorax	< 0.1–0.2	1.5–3.1	N/A
Hemothorax	N/A	0.4–0.6	N/A
Local infection	4.6	1.4	13.2
Blood stream infection	1.8	0.9	6.9

Data from Merrer J, De Jonghe B, Golliot F, et al. Complications of femoral and subclavian venous catheterization in critically ill patients: a randomized controlled trial. *JAMA*. 2001; 286:700–707; Sznajder JJ, Zveibil FR, Bitterman H, Weiner P, Bursztein S. Central vein catheterization: failure and complication rates by three percutaneous approaches. *Arch Intern Med*. 1986; 146:259–261; Mansfield PF, Hohn DC, Fornage BD, Gregurich MA, Ota DM. Complications and failures of subclavian-vein catheterization. *N Engl J Med*. 1994; 331:1735–1738; Martin C, Eon B, Auffray JP, Saux P, Gouin F. Axillary or internal jugular central venous catheterization. *Crit Care Med*. 1990; 18:400–402; Durbec O, Viviani X, Potie F, Vialat R, Albanese J, Martin C. A prospective evaluation of the use of femoral venous catheters in critically ill adults. *Crit Care Med*. 1997; 25:1986–1989; Timsit JF, Bruneel F, Cheval C, et al. Use of tunneled femoral catheters to prevent catheter-related infection: a randomized, controlled trial. *Ann Intern Med*. 1999; 130:729–735.

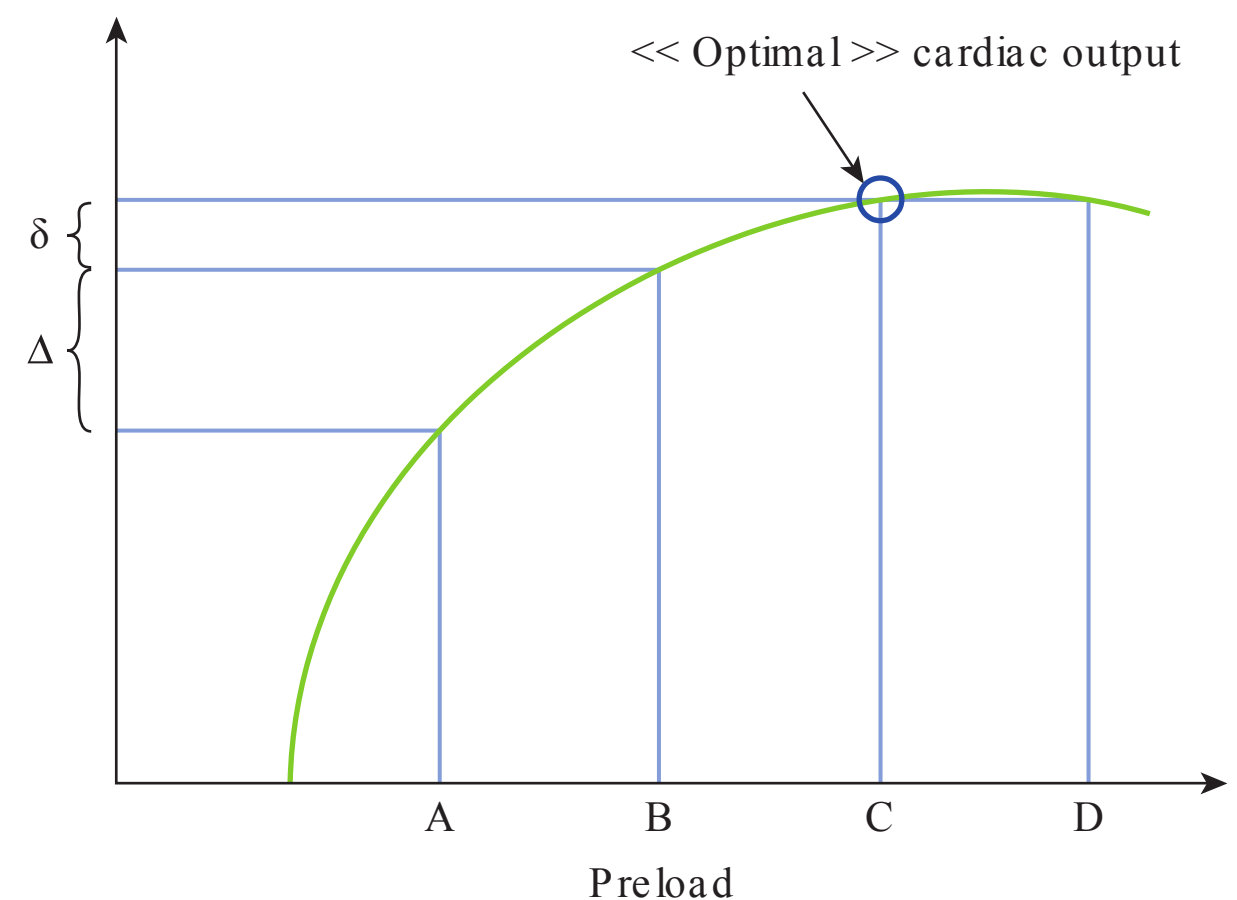


FIGURE 15-5 Starling's cardiac function curve. An increase in preload increases cardiac output until *optimal cardiac output* is reached (preload dependent). Initial preload increases (A to B) result in greater changes (Δ), while additional increases (B to C) have a lesser effect on cardiac output (δ). Further increases in preload beyond this point (C to D) will not result in increased cardiac output (preload independent) and may result in fluid overload and pulmonary edema.

to estimate CO.¹¹ Additionally, CO does not have “normal values,” but varies according to metabolic demand.

Monitoring CO helps guide treatment and response in the unstable patient. An increase in CO of > 15% after a fluid challenge has been considered the gold standard reflecting fluid responsiveness.²⁸ Continued fluid boluses when CO does not increase can result in fluid overload and pulmonary edema. Determining the endpoint of fluid responsiveness allows optimization of CO, blood pressure, and organ perfusion. This relationship is depicted by Starling's law (Figure 15-5).⁴² Thus, the focus in resuscitation should be a relative change in CO in response to therapy rather than a specific CO value.

Venous return related to respiratory changes in the mechanically ventilated patient displays several predictable changes in vena caval diameters, pulmonary blood flow, and left ventricular (LV) output. In the *volume-responsive* patient, increasing intrathoracic pressure during positive-pressure inspiration decreases the pressure gradient for venous return. This results in narrowing of the vena cava, decrease in pulmonary blood flow, and a three- to four-beat phase lag decrease in LV stroke volume and arterial pulse pressure.²

This cyclic variation in stroke volume and arterial pulse pressure is termed pulse pressure variation (PPV) and reflects volume responsiveness. A PPV greater than 13% predicts a greater than 15% increase in CO after a 500-mL crystalloid bolus.⁴³ In high-risk surgery patients, fluid administration until the PPV decreased to less than 10% demonstrated improved outcome with decreased length of hospital stay.⁴⁴ However, for PPV to be accurate, the patient must be intubated and sedated so that respirations are fully synchronized with the ventilator, and without any significant dysrhythmias.²⁵

In spontaneously breathing patients, postural changes such as passive leg raising (PLR) can assess volume responsiveness.

The legs are raised to 30° above the chest and held for 1 to 2 minutes. This maneuver approximates a blood bolus similar to autotransfusion of 300 mL in a 70-kg patient that persists for approximately 2 to 3 minutes. Changes in heart rate, blood pressure, CVP, or CO are then observed. Studies have demonstrated that the dynamic increases in CO induced by PLR are as sensitive and specific to predicting volume responsiveness as PPV during positive-pressure mechanical ventilation.^{45,46}

Invasive Measurement

CO is traditionally measured invasively with pulmonary artery catheterization. A pulmonary artery catheter (PAC; Swan–Ganz) is inserted through a large-bore introducer catheter. The PAC has a thermistor (to sense changes in temperature) located 4 cm from the tip, and a proximal port located 30 cm from the tip. CO is measured by injecting cold fluid through the proximal port, and then measuring the change in temperature of the blood over time at the thermistor. A temperature versus time curve is plotted and analyzed by a computer connected to the catheter, providing a *thermodilution* CO (or blood flow rate in liters per minute). Other measurements obtained by the PAC are listed in Table 15-4.

Although earlier studies have demonstrated that PAC usage increases patient risk and utilization of resources,^{47,48} recent meta-analyses have demonstrated no harm, but also no benefit.^{49,50} Given the controversies and risks associated with the PAC, current expert consensus does not recommend the routine use of the PAC in the emergency department.¹¹ However, in patients with suspected pulmonary arterial hypertension, right ventricular dysfunction, or requiring complex fluid management, PA catheterization may still have a role in the intensive care unit.^{11,51}

Complications from PAC insertion are similar to those of central venous catheterization. Additional complications include arrhythmias, cardiac perforation, pulmonary artery or thoracic duct perforation, tricuspid and pulmonary valve injury, knotting of the catheter, dysrhythmia, and heart block.⁵²



TABLE 15-4: Hemodynamic Variables Obtained by the Pulmonary Artery Catheter

- Cardiac output
- Central venous pressure
- Pulmonary artery occlusion pressure (Pulmonary capillary wedge pressure)
- Pulmonary vascular resistance
- Systemic vascular resistance
- Pulmonary artery pressure
- Ventricular stroke work
- Right ventricular end-systolic and end-diastolic volume
- Mixed and central venous oxygen saturation
- Systemic oxygen delivery
- Systemic oxygen consumption

Noninvasive and Minimally Invasive Measurement of CO

To avoid the complications associated with placement of the PAC, several noninvasive hemodynamic monitoring techniques have been developed to monitor CO.⁵³

THORACIC ELECTRICAL BIOIMPEDANCE

Thoracic electrical bioimpedance (TEB) determines CO based on electrical impedance (or resistance) across the chest wall.⁵⁴ Electrodes placed on the chest measure changes in impedance, which reflect changes in blood volume within the thorax. Since the majority of flow through the thorax occurs in the aorta and vena cava, the changes in impedance that occur in the thorax reflect changes in volume and CO within these great vessels. Previous studies have used TEB to guide clinician assessment of ED patients with dyspnea and showed that this technology can improve the physician's differentiation of cardiac from non-cardiac causes of dyspnea, and change the physician's therapeutic plan for these patients.⁵⁵ Although current studies show acceptable correlation to some invasive criterion standard measurement, TEB has some limitations, including a less reliable signal with patient movement, poor contact or placement of the skin electrodes, or any process that increases intrathoracic blood volume.⁵⁶ Additionally, cardiac dysrhythmias can affect TEB readings.

A modification to bioimpedance is *bioreactance* that uses a signal filter to analyze the relative frequency shift of the current across the thoracic cavity between the chest electrodes, rather than the changes in signal amplitude. This results in a greater signal-to-noise ratio, making it less sensitive to patient movement and external interference. Early validation studies concluded that bioreactance has acceptable accuracy,⁵⁷ although a recent review of minimally or non-invasive cardiac output monitoring concluded that bioimpedance devices are less accurate than thermodilution or Doppler-based devices.⁵⁸

ULTRASOUND

The two parameters required to calculate CO using standard ultrasonography in the ED are the left ventricular outflow tract (LVOT) diameter and the velocity time integral (VTI).⁵⁹ The LVOT diameter is the diameter of the aortic outflow tract, which can be calculated by obtaining a parasternal long-axis view (Figure 15-6). The measurement is obtained by measuring the distance from the inner edge to outer edge, where the right aortic valve coronary cusp meets the interventricular septum to where the non-coronary cusp meets the anterior mitral valve leaflet, in a line parallel to the aortic annulus. VTI is an estimation of the distance that a column of blood travels in 1 systolic stroke, or stroke distance. Using ultrasound, the VTI can be measured by obtaining an apical 5-chamber view and then placing a pulsed-wave Doppler cursor near the aortic valve annulus (Figure 15-7). The Doppler signal is then traced using the cardiac software to calculate VTI.

After obtaining the LVOT diameter and VTI, cardiac output can be calculated from the following equation:

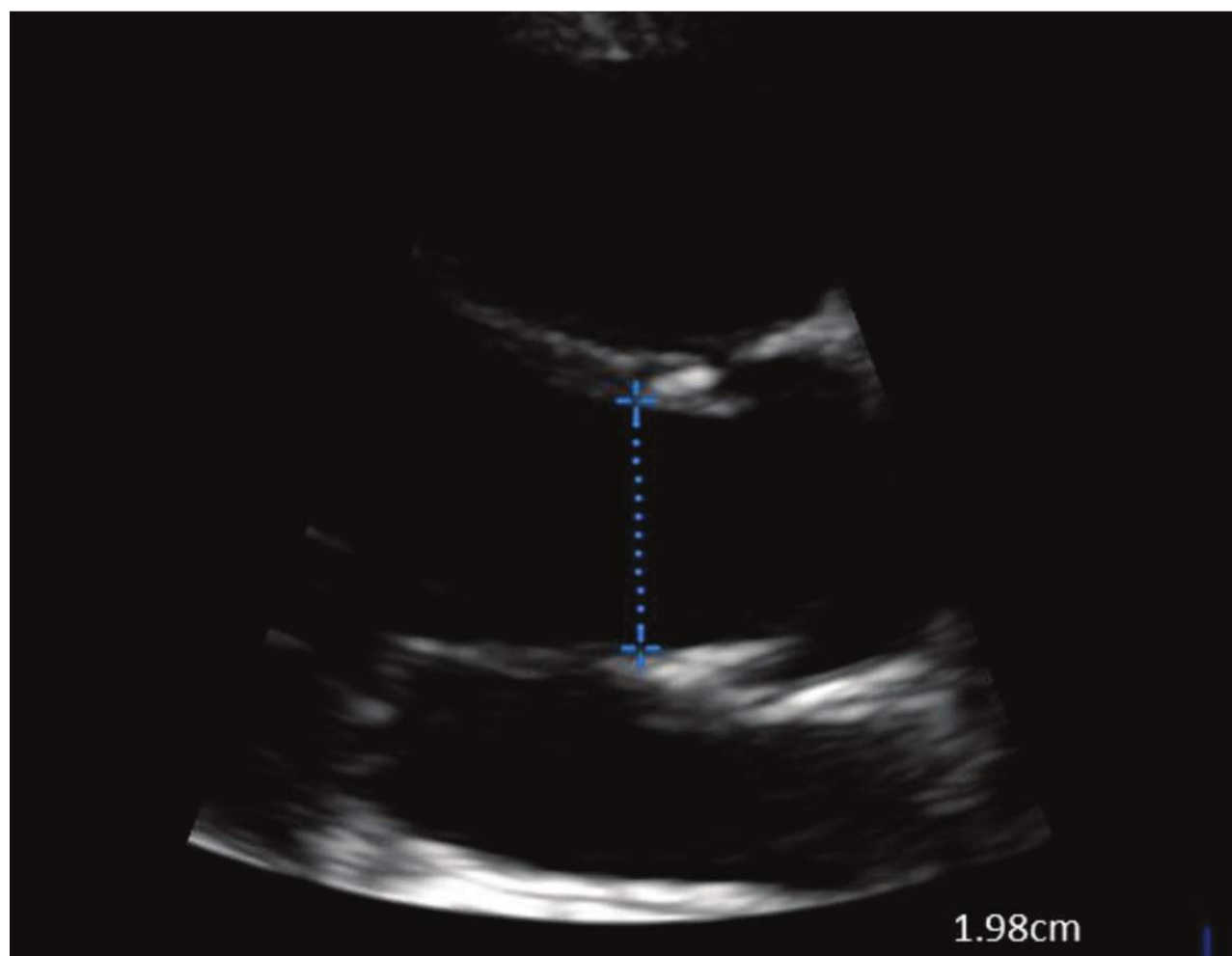


FIGURE 15-6 Measurement of LVOT diameter at aortic valve cusps. This is a parasternal long-axis view on zoom mode with calipers measuring the LVOT diameter at 1.98 cm. This view is obtained by placing the probe at the fourth intercostal space lateral to the left sternum. (Reproduced with permission from Dinh VA, Ko HS, Rao R, Bansal RC, et al: Measuring cardiac index with a focused cardiac examination in the ED, *Am J Emerg Med*. 2012 Nov;30(9):1845–1851.)

$CO = \text{stroke volume (SV)} \times HR$, where $SV = \text{LVOT area} \times \text{stroke distance}$, or $SV = \pi \times (\text{LVOT diameter}/2)^2 \times VTI$. Heart rate is calculated by the ultrasound cardiac software during the VTI measurements or can be input from physical examination or bedside telemetry monitor. If cardiac output

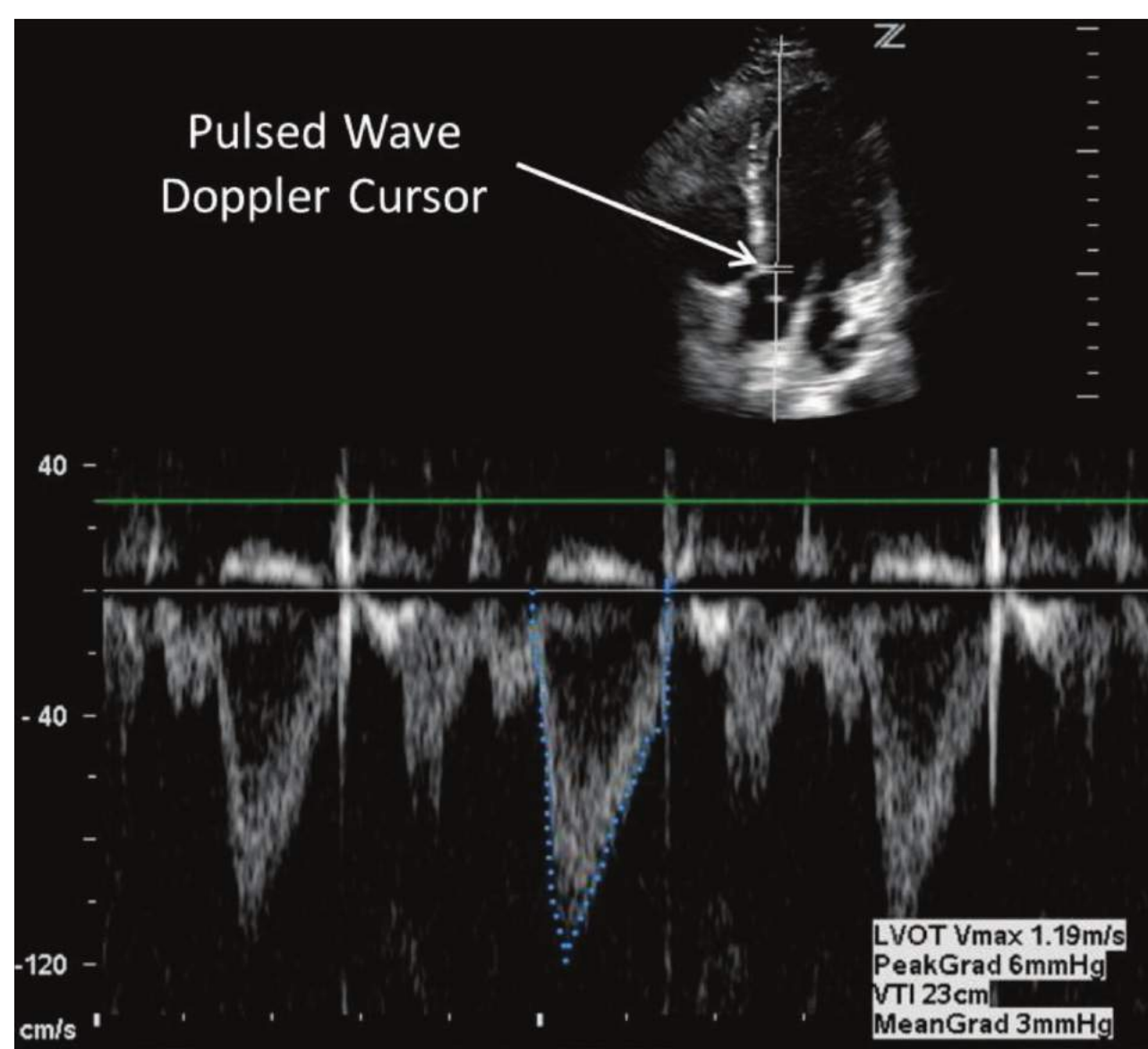


FIGURE 15-7 Measurement of VTI using the apical 5-chamber view. This view is obtained with the apical 4-chamber view and then angulating the probe slightly toward the patient's head until the LVOT can be visualized. The pulsed-wave Doppler cursor is placed at the LVOT, and the Doppler signal is traced (dotted lines) to calculate the VTI. (Reproduced with permission from Dinh VA, Ko HS, Rao R, Bansal RC, et al: Measuring cardiac index with a focused cardiac examination in the ED, *Am J Emerg Med*. 2012 Nov;30(9):1845–1851.)

increases greater than 15% with a fluid challenge then the patient is considered fluid responsive.

ESOPHAGEAL DOPPLER ULTRASOUND

Esophageal Doppler ultrasound (EDUS) is the most-studied technique used in stroke volume optimization studies.⁶⁰ EDUS determines CO by measuring blood flow velocity in the descending aorta to determine stroke volume. A Doppler transducer probe is inserted orally or nasally into the esophagus until its tip is located at the mid-thoracic level and the characteristic signal profile is obtained. The cross-sectional area of the descending aorta is calculated via an algorithm based on the patient's age and body mass index. Using this metric, stroke volume is determined using standard transthoracic Doppler echocardiography.⁶¹ Stroke volume is multiplied by the heart rate to give CO ($CO = \text{stroke volume} \times \text{heart rate}$).

EDUS has high accuracy when compared with the standard PAC in measuring CO.^{58,62,63} In randomized clinical trials, EDUS used in a perioperative resuscitation protocol resulted in optimal fluid resuscitation, decreased hospital length of stay, and decreased postoperative complications when compared with standard therapy.^{64,65} This technology has several limitations, including operator-dependent ability to obtain and maintain the signal, need for frequent repositioning, especially with any patient movement, and discomfort in the non-ventilated patient. However, the use of this technology resulted in none of the complications commonly associated with invasive central venous catheterization, such as pneumothorax or arterial puncture.⁶⁶ In the ED setting, measurements of hemodynamic profile using EDUS resulted in change in shock characterization in 52% of patients, and changes in treatment plans in 68% of patients.⁶⁷

TRANSCUTANEOUS DOPPLER ULTRASOUND

Transcutaneous Doppler ultrasound (TCDUS) is similar to EDUS, except that a handheld probe is placed at the supra-sternal notch with the transducer aimed downward at the aortic valve. Transaortic blood flow velocity profiles are obtained, and CO is calculated from the flow parameters. Recent validation studies comparing TCDUS with PAC measurements of CO showed that the TCDUS measurements have acceptable accuracy.⁶⁸ Interrater reliability for this technology in the ED setting is also adequate.⁶⁹ However, operator training is crucial and may require multiple patient assessments to gain proficiency.⁷⁰

PULSE PRESSURE WAVEFORM ANALYSIS

Pulse pressure waveform analysis provides continuous monitoring of CO. Proprietary algorithms from various manufacturers analyze the arterial pressure waveform (or the pulse contour), obtained from an intra-arterial catheter. Using diastolic pressure as the baseline, the arterial pulse pressure waveform varies as a function of arterial compliance and stroke volume. Stroke volume is estimated by determining the area under the curve of the pulse waveform. Since arterial

compliance varies significantly depending on blood pressure, patient condition, and any medication (e.g., vasopressor usage), the CO measured has to be regularly calibrated with some other reference standard. The two common reference standards for calibration are lithium dilution and transpulmonary thermodilution, which use changes in concentration or temperature over time, similar to the thermodilution method of the PAC.⁷¹ A more advanced algorithm of pulse contour waveform analysis was introduced that does not require calibration with a CO reference standard.⁷² No study has examined the accuracy of these technologies in the ED setting, but in the ICU and operating room, the arterial thermodilution calibrated pulse contour analysis method has been shown to be accurate and sensitive to small dynamic changes in CO, whereas pulse contour analysis without calibration was less validated⁷³ and generally considered to be less accurate than the calibrated devices.⁵⁸

ORGAN OXYGENATION AND PERFUSION MONITORING

The desired end result of hemodynamic monitoring is to improve tissue perfusion. However, optimal hemodynamics do not necessarily equal tissue perfusion. Recent literature has focused on microcirculation and markers of tissue hypoxia. Two methods are readily available to emergency physicians, as well as a number of promising experimental monitoring devices.

Mixed Central Venous Saturation (SvO₂) and Central Venous Oxygen Saturation (ScvO₂)

Venous oxygen saturation monitoring assesses the tissue oxygen extraction and the balance between oxygen delivery (DO₂) and oxygen consumption (VO₂). Normal oxygen extraction ratio (OER) is 25% to 35% and results in a venous oxygen saturation of approximately 70% of arterial DO₂. Venous oxygen saturation is ideally measured in the pulmonary artery as a mixed venous sample (SvO₂). Clinically, SvO₂ reflects the balance between DO₂ and VO₂, with low values reflecting inadequate DO₂ and/or excessive VO₂.

Measurement of SvO₂ requires placement of a PAC, while *central* venous oxygen saturation (ScvO₂) measurement only requires placement of a central venous catheter in the internal jugular or subclavian vein. ScvO₂ can be measured by drawing a standard venous blood gas from the distal port of the central venous catheter and obtaining a *measured* oxygen saturation. Continuous measurement can be performed using specialized catheters and monitors equipped with infrared oximetry and reflection spectrophotometry.

Because ScvO₂ reflects the oxygen balance for the upper portion of the body and does not include venous return from the coronary sinus, a large number of studies have compared ScvO₂ with SvO₂ that reflects the entire body. While ScvO₂ is 2% to 3% less than SvO₂ in healthy individuals, in shock

states, ScvO₂ is typically 5% to 10% *higher* than SvO₂ as blood flow is redistributed from the abdominal vascular beds to the cerebral and coronary circulation.⁷⁴

CLINICAL USE OF ScvO₂

During initial management, despite normalization of vital signs and urine output, global tissue hypoxia may still be present.⁷⁵ ScvO₂ is able to detect occult inadequate DO₂. Regardless of the underlying cause, a low ScvO₂ value represents inadequate DO₂ relative to VO₂.⁷⁶ Understanding that DO₂ is inadequate allows the clinician to focus on the cause. DO₂ is dependent on CO, oxygen saturation, and hemoglobin, whereas VO₂ is increased with heightened metabolic demand. Clinically, hypoxia and anemia are generally easily diagnosed and treated. Thus, a low ScvO₂ can be useful in suggesting that occult low CO may exist, prompting further investigation and treatment.

ScvO₂ (as well as SvO₂) is a global measure of oxygen transport, and does not identify which tissues are hypoperfused. Regional areas of tissue hypoperfusion can be present even with normal ScvO₂ values, particularly in the lower half of the body. Additionally, certain clinical entities (e.g., terminal shock, hypothermia, cyanide poisoning) impair the ability of the tissues to extract oxygen from the blood, leading to decreased OER and high ScvO₂.

Targeting a normal (approximately 70%) SvO₂ as a therapeutic endpoint in the management of ICU patients has not been shown to result in improved outcome.⁴ Inclusion of ScvO₂ monitoring in a treatment protocol, which includes targeting CVP 8–12 mm Hg, MAP > 65 mm Hg, and ScvO₂ > 70%, for severe sepsis and septic shock patients after arrival to the ED (i.e., *early goal-directed therapy*) was shown to result in a significant mortality benefit.^{32,77} A recent multicenter study, however, showed that early identification and resuscitation was the critical intervention with no decrease in mortality associated with the specific targets for CVP and ScvO₂.⁷⁸ These results suggest that emergency medicine physicians must understand when advanced hemodynamic monitoring techniques are necessary to optimize the treatment of critically ill patients.

Lactate

When DO₂ is inadequate to meet tissue oxygen demand, cellular metabolism enters an anaerobic phase. Lactate is a byproduct of anaerobic metabolism and a marker of global tissue hypoxia. Numerous studies have shown that lactate levels above 4 mmol/L (normal < 2 mmol/L) are associated with worse patient outcomes.⁷⁹ More important than a single lactate value is lactate clearance.^{80–83} Multiple studies have demonstrated that the time to lactate clearance is critical, with times > 48 hours resulting in higher morbidity and mortality.⁸¹ Lactate clearance < 24 hours is optimal for increasing survival, as lactate clearance > 24 hours is associated with mortality as high as 90%.^{82,83} However, lactate also increases in disease states other than shock (Table 15-5). Lactate can also have delayed clearance in patients with underlying


TABLE 15-5: Conditions Resulting in Elevated Lactate

Mechanism	Example
Tissue hypoperfusion or hypoxia	Hypotension from any cause Severe anemia Respiratory insufficiency Carbon monoxide poisoning Regional tissue hypoperfusion
Increased oxygen demand	Sepsis Seizure activity Strenuous exercise
Decreased metabolism of pyruvate	Cyanide poisoning Salicylate toxicity Thiamine deficiency Inborn errors of metabolism
Delayed clearance	Renal or hepatic dysfunction

liver disease due to impaired hepatic clearance. In the ED, the ability to decrease lactate as early as 6 hours in patients with severe sepsis or septic shock is associated with increased 60-day survival.^{80,84}

Experimental Monitoring Techniques

Central venous oxygen saturation and lactate are measures of global hypoxia. With the current interest in assessing microcirculation, new technologies are continuously being developed and refined.⁸⁵ While these techniques remain investigational, near-infrared spectroscopy to measure peripheral tissue oxygenation has received much attention in the literature.^{86–88} Near-infrared resonance spectroscopy (NIRS) uses infrared and near-infrared spectrum light to measure the difference in light absorption of oxygenated hemoglobin versus total hemoglobin in a tissue. Based on the theory that peripheral vascular resistance is the first physiologic variable to increase in tissue hypoperfusion and the last to show reperfusion during resuscitation, tissue oxygen saturation (StO₂) can alert the practitioner to low perfusion states as well as guide resuscitation efforts.^{89–92} NIRS is non-invasive and easy to apply in the critically ill patient. However, current literature has not demonstrated a cause-and-effect relationship in the use of StO₂ measurements and outcome.⁹³

Other investigational modalities include orthogonal polarization spectroscopy (OPS), sublingual partial pressure of carbon dioxide (PslCO₂), partial rebreathing,⁵⁸ exhaled CO₂ method, waveform capnometry,⁶⁰ videomicroscopy,⁹⁴ and transcutaneous oxygen tension.⁹⁰ Further investigation is required before they can reliably be used in the care of critically ill patients.

SUMMARY

Emergency physicians are managing greater numbers of critically ill patients, and for longer periods of time. Hemodynamic monitoring is used to identify cardiovascular instability, help

determine etiology, and guide effective therapy. While no single hemodynamic variable should be used as an absolute target, understanding what modalities are available, how to optimize patient diagnosis and treatments, and understanding the overall hemodynamic changes in response to therapies can reduce patient morbidity and mortality.

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Acute Coronary Syndrome

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INTRODUCTION

Acute coronary syndrome (ACS) is not a single diagnosis but a spectrum of disease. It encompasses ST-segment elevation myocardial infarction (STEMI), non-ST-segment elevation myocardial infarction (NSTEMI), and unstable angina (UA). It is a disease process that, if unrecognized, imparts upon the patient profound morbidity, if not mortality. In fact, acute myocardial infarction is the leading cause of death in the United States, if not the entire developed world.¹ For these reasons, ACS should be respected and treated expeditiously and aggressively.

EPIDEMIOLOGY

In the United States, coronary heart disease (CHD) resulted in 735,00 people suffering myocardial infarction in 2011, of whom 120,000 died. Of those, an estimated 635,000 Americans had a new coronary event while 300,000 had a recurrent one.² CHD includes ACS as well as UA. While stable angina is an important condition, it is not a focus of this discussion because on its own, it is not directly responsible for mortality statistics (although a small number of deaths due to CHD are coded as being from angina pectoris). With respect to mortality, one in every seven deaths in the United States in 2011 was due to CHD with an American suffering a coronary event once every 43 seconds and one American dying every ninety seconds as a result of a myocardial infarction.² The 2011 estimated cost of caring for these patients was \$320.1 billion.² The prevalence of ACS is expected to continue to climb as increasing numbers of patients are being diagnosed

with NSTEMI and UA. This is not solely due to the aging of the population but also due to utilization of more sensitive diagnostic tests, increased availability of early invasive therapies, and treatment of comorbid conditions early and aggressively that delay the progression of disease to STEMI.³⁻⁵

With a heightened level of concern and recognition of these clinical entities, fewer patients have gone unrecognized. Consequently, mortality related to ACS has declined dramatically, particularly for STEMI. Unfortunately, the rate of decline has not been as great for NSTEMI and UA. This is likely due to a delay in the implementation of treatment guidelines for patients with these conditions.^{2,6,7}

PATHOPHYSIOLOGY

Understanding acute myocardial infarction requires understanding the pathophysiology of coronary artery thrombosis. While ACS can be caused by an embolic obstruction, this is much less common than ACS caused by atherosclerotic disease. There are two general types of atherosclerotic plaque, stable and unstable, and each produces a different presentation of ACS (see Figure 16-1). The stable plaque has a thick fibrous cap that slowly thickens and produces the symptoms of classic angina such as progressively worsening exertional chest tightness. In this situation, oxygen delivery to the myocardium is gradually diminished, producing decreased tolerance of myocardial stress. Unstable plaques, however, have a thin fibrous cap suffused with inflammatory cells that make the plaques vulnerable to rupture. ACS associated with acute plaque rupture produces a spectrum of findings based on the location and degree of associated thrombosis and

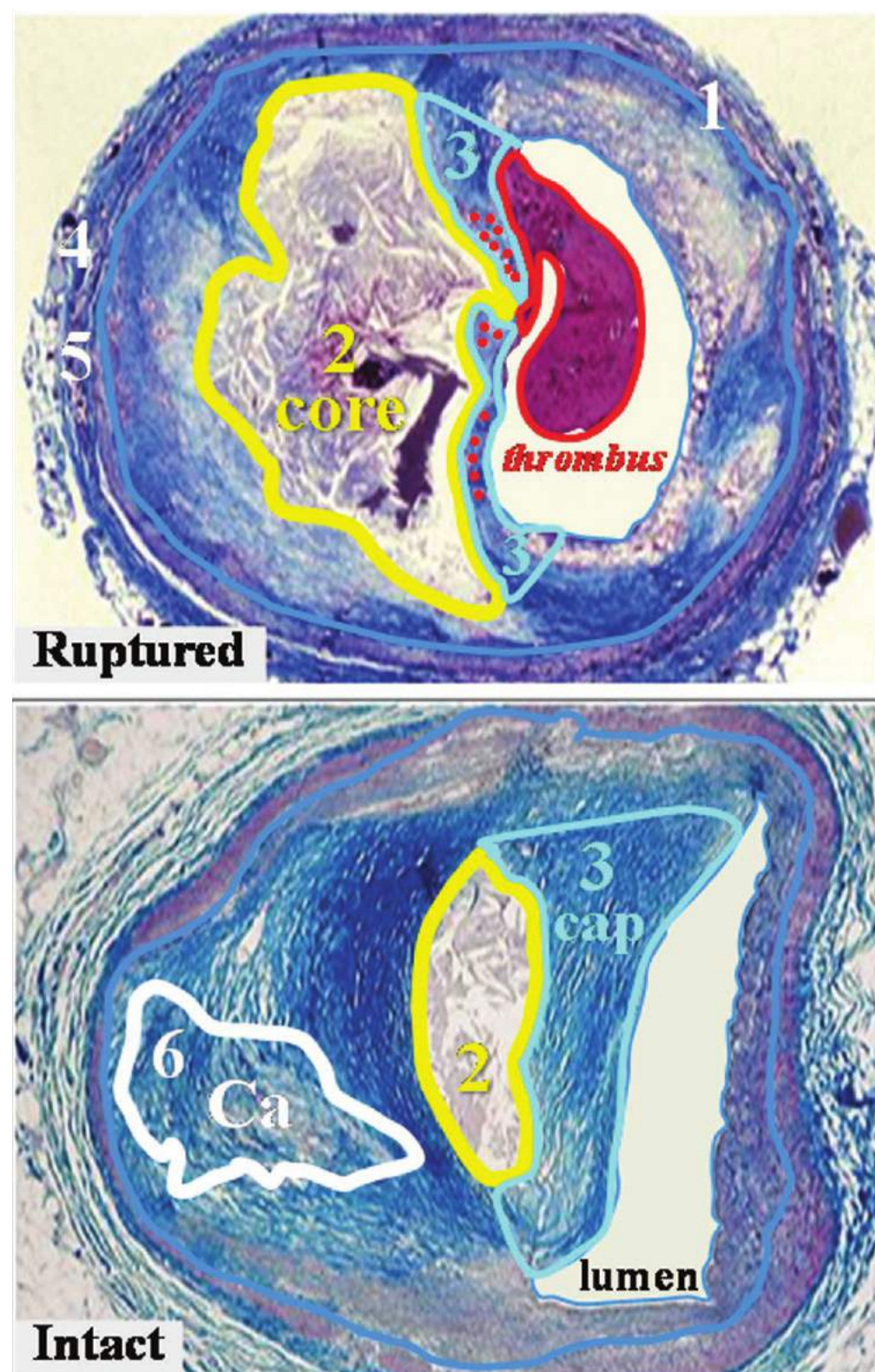


FIGURE 16-1 Plaque rupture and determinants of vulnerability. For comparison, a “thin-capped” ruptured plaque with thrombus (top) and an intact, “thick-capped” stable plaque (bottom) are depicted. Vulnerable plaque features are listed to the right.

Coronary plaque rupture

1. Plaque size

- Paradoxical remodeling (stenosis ↓)

2. Necrotic core

- ~34% of plaque area*
- ~3.8 mm² and ~9 mm long*

3. Fibrous cap

- Thickness ↓, ~23 μm (95% <65 μm)*
- Macrophages (·) ↑, ~26% of cap*
- Smooth muscle cells ↓
- Apoptosis ↑
- Thrombus

4. Neovascularization

- Intraplaque hemorrhage ↑

5. Perivascular inflammation

6. Calcification and “spotty”

consequent impairment of oxygen delivery. A small thrombus can produce anginal symptoms while a higher-degree occlusion produces similar symptoms with NSTEMI. Complete occlusion can produce frank STEMI of differing severity depending on the amount and location of myocardium affected. Many of the treatments for ACS focus on maximizing oxygen delivery while minimizing platelet activation, aggregation, and clotting.⁸

PRESENTATION

With respect to ACS, certain risk factors have been associated with the probability of developing cardiac disease over a lifetime but have been shown to be of little utility in the acute setting.⁹ Age, sex, family history, hypertension, diabetes mellitus, elevated cholesterol, obesity, smoking, and physical inactivity, while important, are not predictive of acute disease. One of the more common tools for risk stratifying patients with suspected ACS is the Thrombolysis In Myocardial Infarction (TIMI) score (Table 16-1).

Associated with each score is a specific risk of poor outcome defined as death, myocardial infarction, or need for acute percutaneous coronary intervention (PCI). In one study, a score of 3 or higher equates to a high risk, with one study showing 5% mortality at 14 days and an 8% chance of needing PCI¹⁰ (Table 16-2). Current AHA recommendations suggest that risk scores, such as TIMI or GRACE, should be utilized in the initial evaluation of these patients.²⁸

As with most diagnoses, an accurate history and thorough physical examination are necessary to generate a broad and appropriate differential as well as an accurate diagnosis. Unfortunately, there is no way to effectively rule out ACS by history and physical examination alone. Some patients present in a way classically referred to as “typical”: poorly localized chest pain or pressure radiating to the left jaw, both shoulders, or left upper extremity; intermittent in nature; lasting 15 to 20 minutes at a time; exacerbated or precipitated by physical activity; relieved by rest or nitroglycerin; and associated with diaphoresis and shortness of breath. Unfortunately, most patients do not present in such a typical



TABLE 16-1: TIMI Risk Factors (1 Point Each)

- Age 65 and above
- At least three risk factors for CAD (HTN, DM, elevated cholesterol, family history, tobacco use)
- Prior coronary stenosis of 50% or more
- ST-segment deviation
- At least two anginal events in preceding 24 h
- Use of aspirin in past 7 days
- Elevated serum cardiac enzymes (CK-MB; troponin)

Adapted with permission from Pollack CV Jr, Sites FD, Shofer FS, et al. Application of the TIMI risk score for unstable angina and non-ST elevation acute coronary syndrome to an unselected emergency department chest pain population, *Acad Emerg Med*. 2006 Jan;13(1):13–18.


TABLE 16-2: Thirty-Day Probability of Poor Outcome Based on TIMI Score

TIMI Score 0	2.1%
TIMI Score 1	5%
TIMI Score 2	10.1%
TIMI Score 3	19.5%
TIMI Score 4	22.1%
TIMI Score 5	39.2%
TIMI Score 6	45%
TIMI Score 7	100%

Adapted with permission from Pollack CV Jr, Sites FD, Shofer FS, et al. Application of the TIMI risk score for unstable angina and non-ST elevation acute coronary syndrome to an unselected emergency department chest pain population, *Acad Emerg Med*. 2006 Jan;13(1):13–18.

manner. Furthermore, certain patient populations, most notably women, the elderly, and diabetics, present with what has been termed “anginal equivalent.”

These symptoms may include isolated jaw, neck, shoulder, back, arm, or epigastric discomfort, as well as nausea, vomiting, dizziness, generalized fatigue, or weakness. Even subtler, a patient may simply describe an increasing difficulty with performing his or her activities of daily living. Those with cognitive impairment, diabetics, and substance abusers may present with altered mental status. It is absolutely critical to remember that the diagnosis of UA may be based on history and physical examination alone, despite a normal electrocardiogram (ECG) or negative cardiac biomarker testing.

Physical examination for patients with ACS is most useful for evaluating other potential etiologies of the patient’s complaint, although the exam has utility in predicting patients who may be at risk for a poorer outcome or who have developed a complication related to their myocardial infarction. For example, findings of unstable vital signs, jugular venous distention, pulmonary edema, and/or an S3 gallop are indicative of acute heart failure. A new murmur is suggestive of papillary muscle rupture. Hemiparesis can indicate aortic dissection. Each of these is associated with worse prognosis than ACS patients without these complications. Caution must be exhibited, though, when it comes to physical examination and the possibility of ascribing a patient’s symptoms to a process more benign than ACS. For example, a significant proportion of ACS patients may in fact have pleuritic, positional, or reproducible chest pain on examination.¹¹ Simply stated, there is no single feature of the physical examination that safely rules out ACS.

DIAGNOSTIC APPROACH

The most crucial diagnostic study in any patient suspected of having ACS is the ECG. It should be obtained within 10 minutes of the patient’s arrival to the emergency department (ED) or similarly within minutes after the development of chest pain if the patient is already hospitalized. It is vital to the patient’s outcome that the ECG be completed and accurately interpreted in a timely manner. Also, the patient should be placed on a cardiac monitor as soon as possible. For the

inpatient who develops chest pain in a non-monitored setting, this may require transfer to a telemetry unit or ICU depending on the result of the ECG. One way to understand the correspondence between ECG findings and diagnosis is demonstrated in Figure 16-2.

If a STEMI is identified, appropriate resources should be immediately mobilized and interventions undertaken.^{12,13} STEMI diagnostic criteria, as described by the American College of Cardiology (ACC) and American Heart Association (AHA), are outlined in Table 16-3.¹⁴ Three types of ST-segment changes are pictured in Figure 16-3. Figure 16-4 demonstrates ECG patterns corresponding with specific anatomic regions. Reciprocal ST-segment changes, such as depressions in opposite leads or findings on right-sided or posterior ECGs, make the diagnosis of STEMI more specific. While these criteria have been established and accepted, an ECG with these findings is still only 75% sensitive and 69% specific for STEMI.¹⁵ Of course, there are several other conditions that may mimic STEMI by causing ST-segment elevations such as pericarditis, early repolarization, left ventricular hypertrophy, or prior myocardial infarction with resultant ventricular aneurysm. Some examples of these are pictured in Figure 16-5.

As it relates to NSTEMI, the ECG is perhaps of equal importance in the detection of ischemia, but 1% to 5% of patients with a myocardial infarction will have a completely normal ECG at the time of presentation.¹⁶ Therefore, serial ECGs are of tremendous value when considering a diagnosis of ACS and should be obtained with subsequent episodes of chest pain and with repeat cardiac biomarker testing. In fact, dynamic ECG changes associated with intermittent episodes of chest pain are most predictive of ACS. According to the ACC and AHA, ST-segment depressions greater than 0.05 mV with or without T-wave inversions are the most concerning findings associated with a poor outcome in NSTEMI patients. Thirty-day mortality of patients with isolated ST-segment depressions is equivalent to those with ST-segment elevations. T-wave inversions ≥ 0.2 mV were next most concerning. Finally, ST-segment depressions and T-wave inversions of lesser magnitude or T waves newly upright (pseudonormalized) were found to be less concerning, but still clinically significant with regard to outcome.¹⁶

The necessity of accurate ECG interpretation cannot be overstated. A retrospective study of 1684 patients with


TABLE 16-3: AHA/ACC STEMI Diagnostic Criteria

ST-segment elevation ≥ 1 mm (0.1 mV) in two or more adjacent limb leads (from AVL to III, including -aVR)
ST-segment elevation ≥ 1 mm (0.1 mV) in precordial leads V_4 – V_6
ST-segment elevation ≥ 2 mm (0.2 mV) in precordial leads V_1 – V_3
Left bundle branch block with signs of ischemia (Sgarbossa criteria)

Data from Wagner GS, Macfarlane P, Wellens H, et al: AHA/ACC/HRS Recommendations for the Standardization and Interpretation of the Electrocardiogram: Part VI: Acute Ischemia/Infarction, *Circulation*. 2009 Mar 17;119(10):e262–e270. Note: Any one of the criteria indicates STEMI.

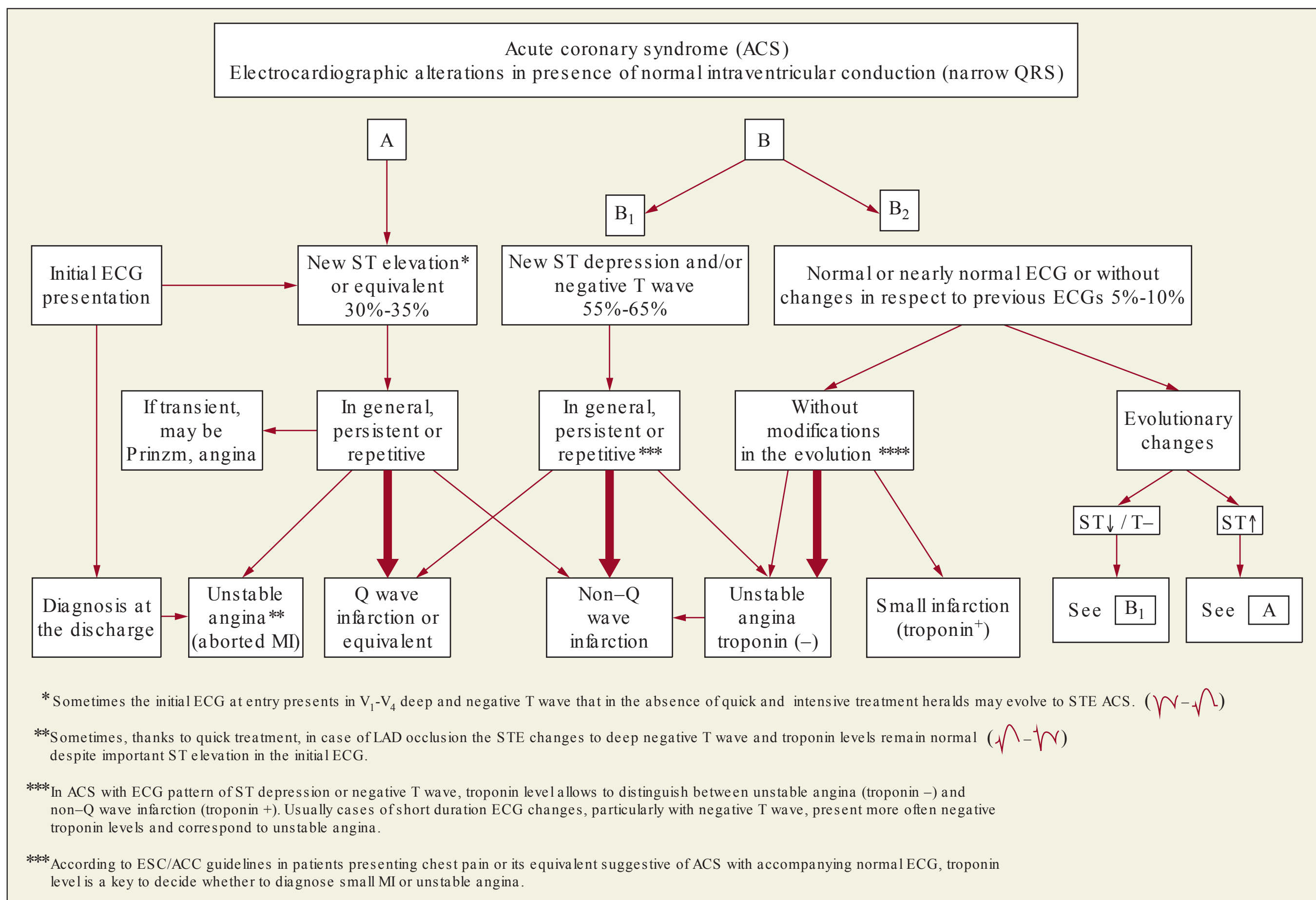
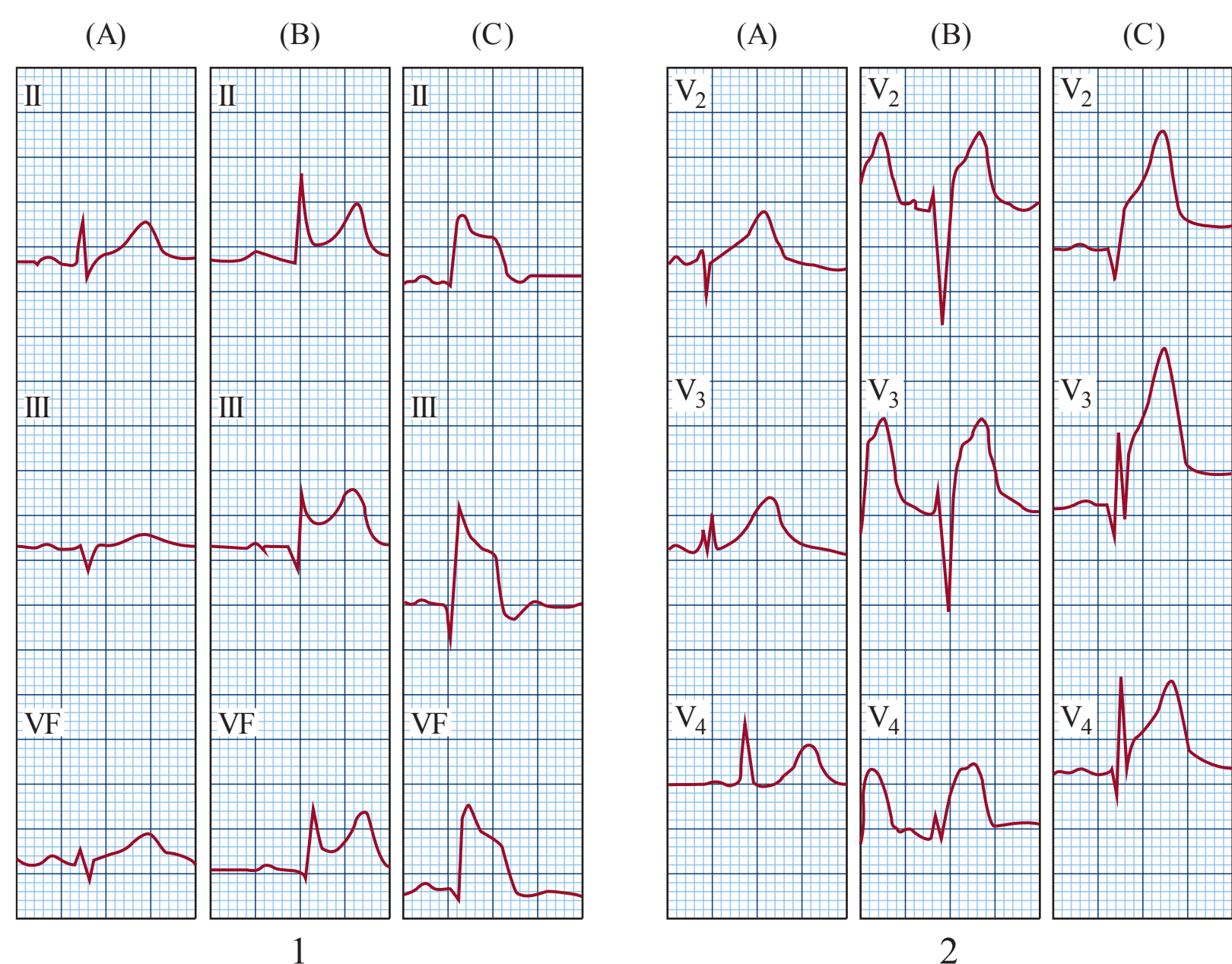


FIGURE 16-2 ECG alterations observed in patients with acute coronary syndromes presenting with narrow QRS and without confounding factors such as left ventricular hypertrophy (LVH). Observe the initial ECG presentation: **(A)** ST-segment elevation or equivalent; **(B)** Non-ST-segment elevation; **(B₁)** ST-segment depression/negative T wave; and **(B₂)** normal or nearly normal ECG or without changes in respect to previous ECG with its approximate incidence and final discharge diagnosis according the evolution.

FIGURE 16-3 1. The three types of repolarization abnormalities that may be seen in an acute phase of myocardial infarction involving the inferolateral zone: **(A)** tall and/or wide T waves in inferior leads; **(B)** abnormal ST-segment elevation, with no changes of the final part of QRS; and **(C)** important ST-segment elevation and distortion of the final part of QRS. **2.** The three types of repolarization abnormalities that may be seen in an acute phase of myocardial infarction involving the anteroseptal zone wall: **(A)** tall and/or wide T waves especially seen in right precordial leads; **(B)** abnormal ST-segment elevation, with no changes of the final part of QRS; and **(C)** important ST-segment elevation and distortion of the final part of QRS.



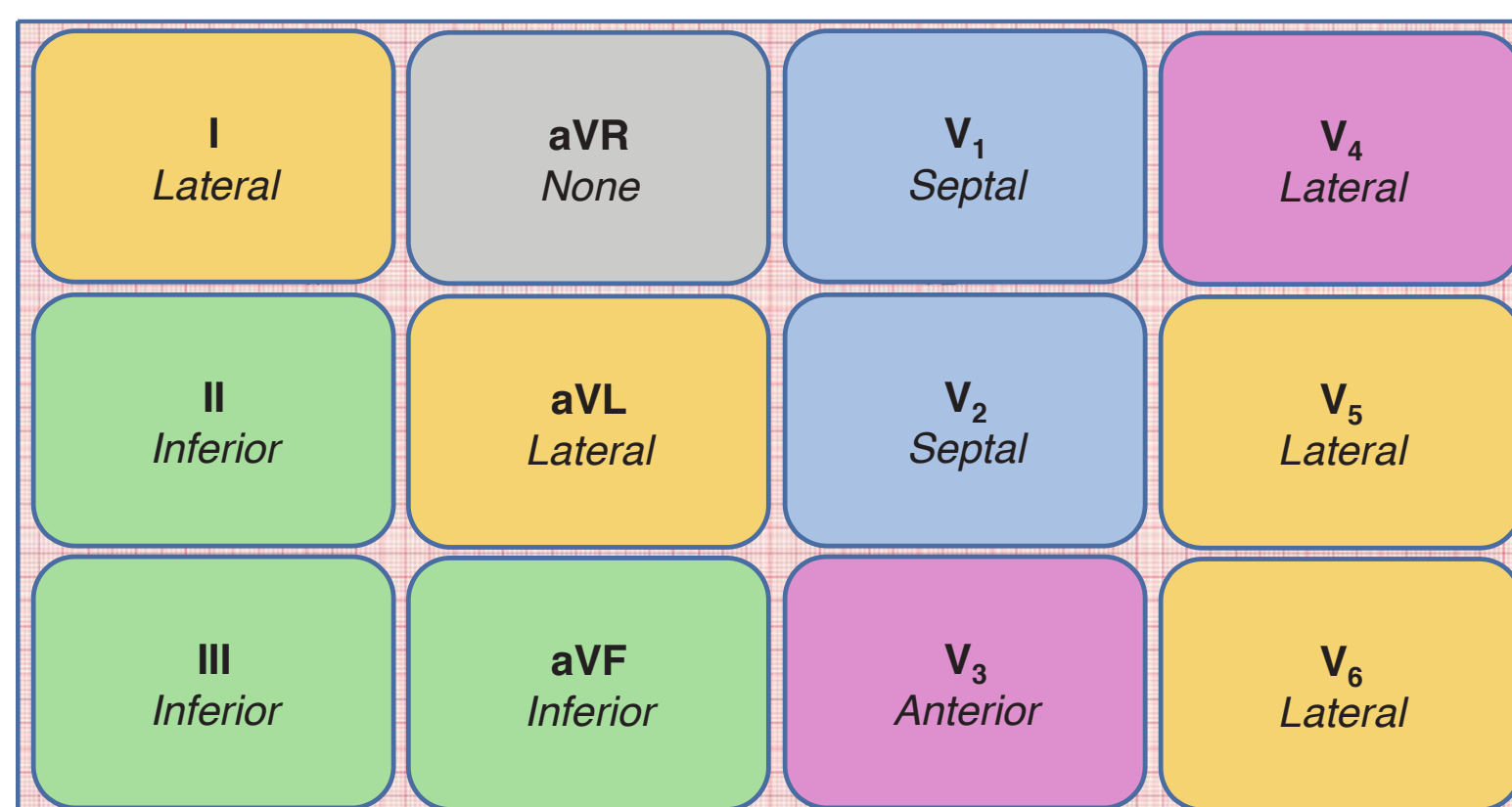


FIGURE 16-4 The anatomic regions represented by a standard 12-lead electrocardiogram.

an acute myocardial infarction revealed that 12% of those patients presenting to the ED with active, ongoing ischemia, identifiable by ECG analysis, were missed.¹⁷ While not statistically significant, there was a trend toward increased in-hospital mortality as a result.

In certain instances, the ECG may be more difficult to interpret. One such example is in the setting of left bundle branch block (LBBB). The Sgarbossa criteria have been validated as being highly specific for a patient having a STEMI who has an LBBB (see Table 16-4 and Figure 16-6).¹⁸ The more criteria met, the more likely a STEMI is occurring. A score of 5 to 10 indicates an 88% to 99% probability of an acute STEMI. But even with 0 points, there still exists a 16% chance of an acute STEMI. Because of the low sensitivity of the Sgarbossa criteria when there are < 10 points, the ECG cannot be used alone to exclude ACS in a patient with chest pain and a preexisting LBBB. A truly new LBBB, identified by a recent ECG without an LBBB, is also cause for substantial concern and has been included as an indicator of STEMI in prior guidelines.

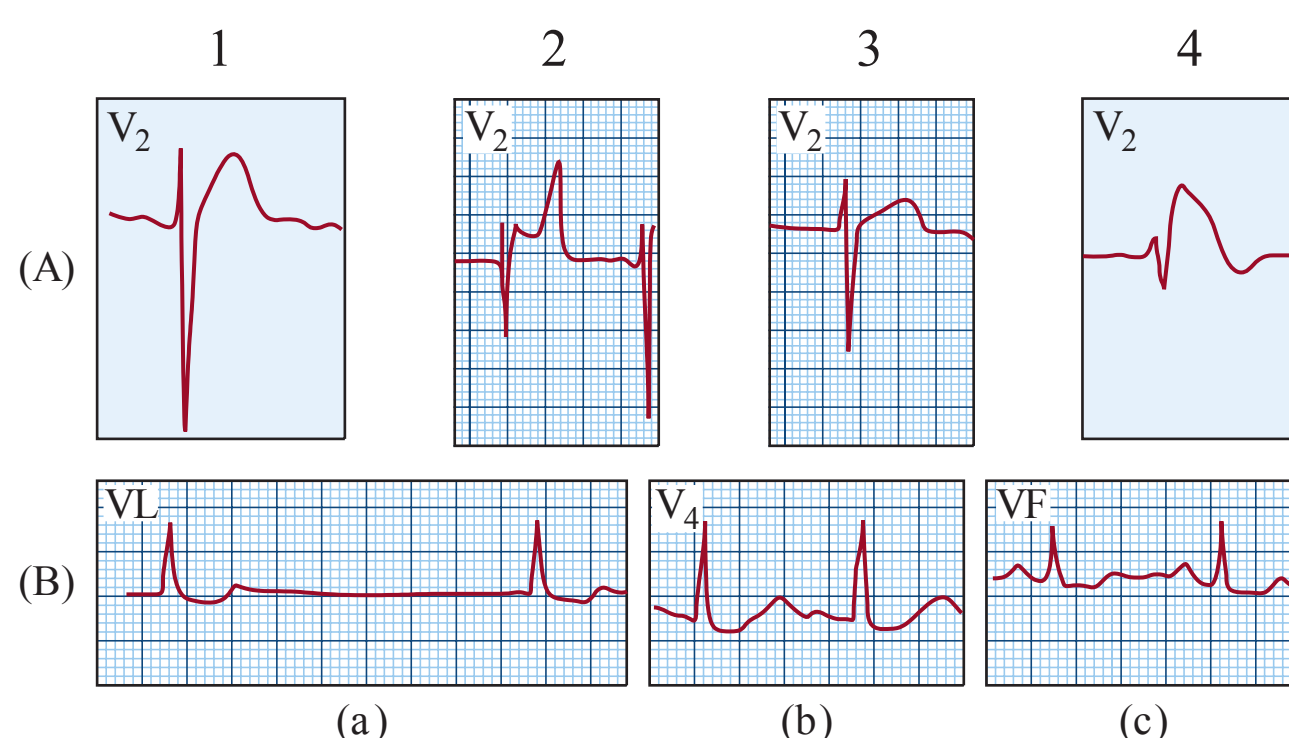


FIGURE 16-5 **A.** The most frequent cases of ST-segment elevation apart from ischemic heart disease: (1) pericarditis; (2) hyperkalemia; (3) athletes; and (4) typical Brugada pattern with coved ST-segment elevation. The saddle-type variant of Brugada syndrome has to be differentiated from the normal variant. **B.** ST-segment depression due to causes other than ischemia: (1) digitalis effect (note the typical morphology with ST depression and short QT in patients with slow atrial fibrillation); (2) hypokalemia in a patient with congestive heart failure taking high doses of furosemide; and (3) mitral valve prolapse.

In addition to electrocardiography, serum biomarker analysis is an essential tool in the setting of NSTEMI. While useful in STEMI as well, biomarkers play a less important role as treatment should be started based on the ECG alone. As stated earlier, UA is a diagnosis made by history, physical examination, and a consideration of alternative diagnoses by generating an appropriate differential and excluding other etiologies. One may expect an unremarkable ECG and negative serum cardiac biomarker analysis in the setting of UA. Like STEMI and NSTEMI, UA is a diagnosis one cannot afford to miss. These patients still require aggressive management as they may unpredictably progress to NSTEMI or STEMI.

Serum cardiac biomarker analysis allows for diagnostic confirmation as well as risk stratification, as patients with positive results have a higher complication rate.^{19,20,22} Historically, the most commonly used biomarkers included creatine kinase-myocardial band (CK-MB), myoglobin, and troponin T or I. The ACC and AHA guidelines no longer recommend the use of myoglobin or CK-MB in the evaluation of patients suspected of having NSTEMI. Both these markers can be sensitive early in the course of the disease process, but do not provide any additional information when used with troponin testing. In contrast, troponin is both sensitive and specific when it comes to myocardial infarction. Troponin levels rise 2 to 4 hours after an ischemic event with peak levels seen 15 to 20 hours after the event. Troponin levels remain elevated for up to 10 days.

Due to its high degree of specificity and the ability of diagnostic equipment to detect even scant troponin elevations



TABLE 16-4: Sgarbossa Criteria and Point Assignment

ST-segment elevation ≥ 1 mm in a lead concordant with a QRS complex	5 points
ST-segment depression ≥ 1 mm in V ₁ , V ₂ , or V ₃	3 points
ST-segment elevation ≥ 5 mm in a lead discordant with a QRS complex	2 points

Adapted with permission from Sgarbossa EB, Pinski SL, Barbagelata A, et al: Electrocardiographic diagnosis of evolving acute myocardial infarction in the presence of left bundle-branch block. GUSTO-1 (Global Utilization of Streptokinase and Tissue Plasminogen Activator for Occluded Coronary Arteries) Investigators, *N Engl J Med*. 1996 Feb 22;334(8):481–487.

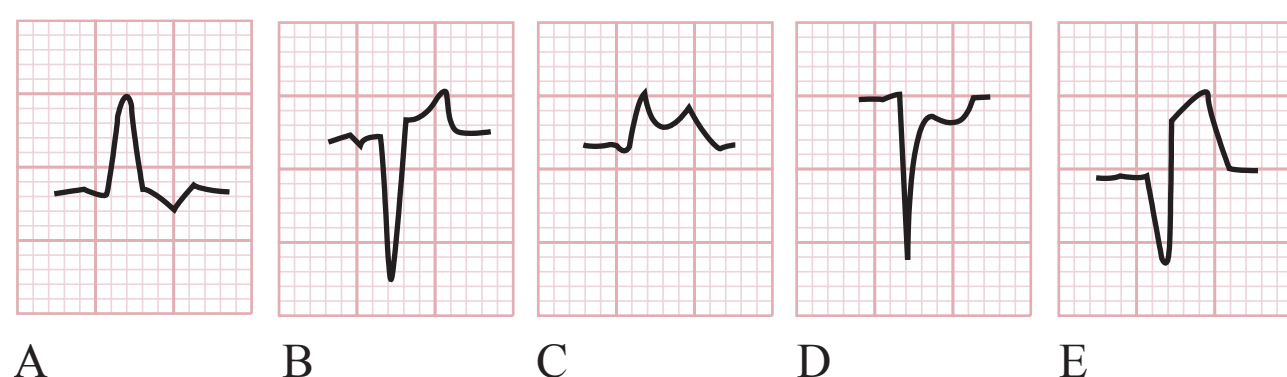


FIGURE 16-6 Discordant and concordant ST elevation and depression in the setting of left bundle-branch block. ST segment abnormalities in left bundle-branch block. **A.** Discordant ST segment depression (“normal”). **B.** Discordant ST-segment elevation (“normal”). **C.** Concordant ST-segment elevation [strongly suggestive of acute myocardial infarction (AMI)]. **D.** Concordant ST segment depression (suggestive of AMI). **E.** Excessive (> 5 mm) discordant ST-segment elevation (weakly suggestive of AMI). (Reproduced with permission from Holstege C, Baer A, Pines J, et al: *Visual Diagnosis in Emergency and Critical Care Medicine*, 2nd edition. West Sussex: Wiley-Blackwell;2011.)

(particularly when utilizing high-sensitivity troponin testing), both the prevalence and incidence of ACS have increased dramatically.¹⁴ Of course, compared to negative biomarkers, even small elevations identify patients at greater risk who may benefit from more aggressive intervention. There are other reasons a patient may have an elevated troponin, such as renal failure (which affects troponin I less than T), trauma, congestive heart failure (CHF), and sepsis, but each of these patients, as a consequence of his or her comorbidity, is at even greater risk and possesses a higher mortality if the elevation is due to cardiac ischemia.²¹

As with any biomarker, serial measurements are more useful than any single measurement. A recent study of chest pain patients utilized high-sensitivity cardiac troponin T measurements which were repeated after 2 hours. This study demonstrated a very high sensitivity and specificity for the detection of ACS and accurate triage of these patients.²² Despite the very high sensitivity of these newer troponin assays, we are not yet at a point where a single biomarker measurement can accurately predict outcome.¹⁹

There have been several other novel biomarkers studied including proBNP, CRP, ischemia-modified albumin, copeptin, heart-type fatty acid binding protein, and homocysteine, but none are recommended by the AHA or ACC for the evaluation of ACS in the acute setting.

In addition to ECG and cardiac biomarker analysis, various other modalities may be utilized for evaluating the cardiac patient. In the appropriate setting, provocative testing via exercise stress testing with or without myocardial perfusion imaging and stress echocardiography are being utilized in an effort to evaluate patients for ACS with higher certainty to allow for safer discharge. Similarly, echocardiography during an acute episode of ACS can evaluate the myocardium for wall motion abnormalities. An experienced cardiac sonographer can detect changes from the normal symmetric contraction of the myocardium that may indicate cardiac stunning associated with acute ischemia.

Computed tomography (CT) has been and is still currently being investigated as an alternative to coronary angiography with the benefit of being less invasive and perhaps more readily available. Cardiac computed tomography (CCT) is a modality by which the degree of calcification of coronary

arteries is measured without the need for intravenous contrast. A greater degrees of calcification, reported as a calcium score, is indicative of a higher likelihood of a future coronary event and the chance of an obstructive lesion in need of intervention.²³ It does not evaluate the true cardiac lumen, however, and the score generated by such measurement reflects only relative or overall risk and not absolute risk or the certainty of an obstructing lesion being present.²⁴

Unlike CCT, cardiac CT angiography (CCTA) evaluates the true cardiac lumen by utilizing intravenous contrast and has been shown to correlate well with findings derived from PCI. Less invasive and more readily available than PCI, CCTA is not without risk. Compared with CCT, CCTA adds the risk of exposure to intravenous contrast and involves significantly more radiation than cardiac catheterization. Furthermore, both CCTA and CCT are purely diagnostic tools. So while they may be utilized to safely discharge a certain subgroup of ED patients without need for admission and/or coronary angiography, patients who require intervention will end up receiving significantly more radiation and contrast than if they initially had a traditional cardiac angiogram. The same is true when CCTA is utilized for ED or ICU patients to determine the need for transfer to PCI-capable facilities. Furthermore, to date, published data derived from multiple, randomized, multicenter clinical trials are lacking. An example of at CCTA is presented in Figure 16-7.

Cardiac magnetic resonance imaging (CMR) with or without contrast is another novel diagnostic tool under investigation that has been shown to have a high positive predictive value and specificity for myocardial infarction.²⁵ Images obtained can be synchronized with the cardiac cycle and can combine both angiographic evaluation of the patient's coronary arteries and wall motion abnormalities. Like CT, CMR is also in need of additional study and validation before it can be deemed appropriate for routine clinical use in the ACS patient.

TREATMENT

The mainstay of treatment of the critical patient with ACS is focused on improving oxygen delivery to the myocardium. This is accomplished in four ways: anti-ischemic therapy, antiplatelet therapy, anticoagulation therapy, and reperfusion therapy. Anti-ischemic therapies, such as oxygen, nitroglycerin, and β -blockers, work by matching oxygen delivery and demand and therefore by increasing oxygen delivery or decreasing oxygen demand. Antiplatelet medications, such as aspirin, prevent further thrombosis by minimizing platelet activation and adhesion. Anticoagulants such as heparin inhibit clot formation via the clotting cascade or by direct thrombin inhibition. Reperfusion of ischemic myocardium is accomplished via thrombolytics or PCI, both of which are used to directly restore cardiac circulation. In some cases, these treatments will fail and the patient will require coronary artery bypass grafting (CABG) or, in the case of frank cardiogenic shock, invasive mechanical support such as intra-aortic balloon pump or left ventricular assist device placement, both of which are covered in (please refer to Chapter 21, Left Ventricular Devices).

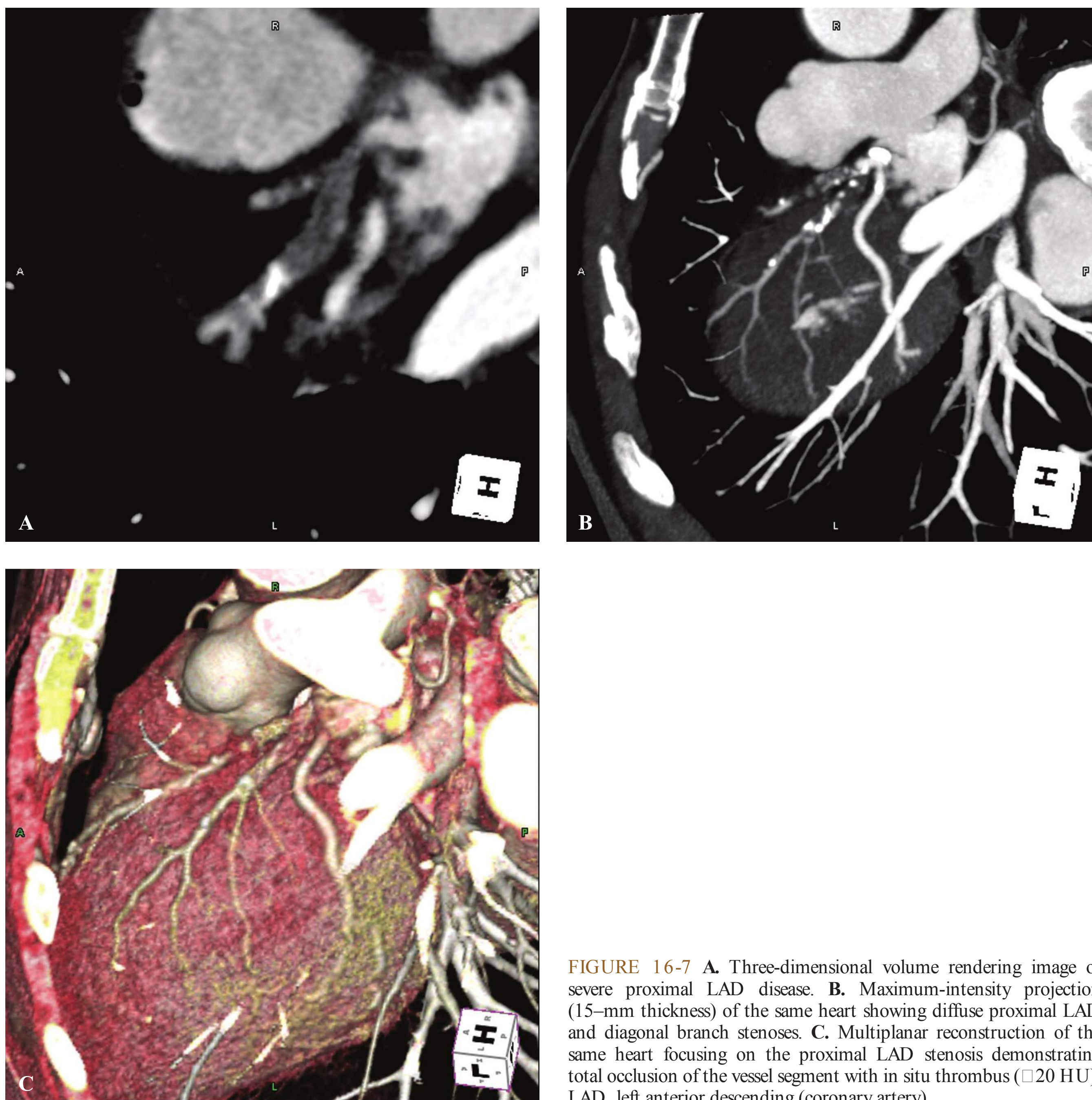


FIGURE 16-7 **A.** Three-dimensional volume rendering image of severe proximal LAD disease. **B.** Maximum-intensity projection (15-mm thickness) of the same heart showing diffuse proximal LAD and diagonal branch stenoses. **C.** Multiplanar reconstruction of the same heart focusing on the proximal LAD stenosis demonstrating total occlusion of the vessel segment with in situ thrombus (\square 20 HU). LAD, left anterior descending (coronary artery).

Anti-Ischemic Therapy

Supplemental oxygen delivery has been a standard treatment for ACS for nearly a century, although the data on its effectiveness are quite thin and inconclusive, and even more recently may suggest harm in patients who have a normal oxygen saturation without the administration of supplemental oxygen.^{26,27} The recommendations from the most recent ACC/AHA guidelines strongly endorse the use of oxygen in all patients with ACS and hypoxia or respiratory distress.²⁸ Oxygen should be used with caution in patients with a history of COPD.

Nitrates, like oxygen, are nearly ubiquitous in the treatment of ACS, although the research on their utility is limited. The largest effect was noted in a meta-analysis of more than 80,000 patients that demonstrated that nearly 300 patients would need to be treated with nitrates to prevent one additional death.²⁹ Nitrates produce arterial and venous dilatation, resulting in decreased cardiac preload and afterload, and subsequently decreased myocardial oxygen demand. Simultaneously, nitrate-induced coronary artery dilation can improve oxygen delivery to the myocardium. Nitrates should be administered initially via a sublingual

route at doses of 0.4 mg, 5 minutes apart, for a total of three doses. If anginal symptoms persist after these doses, an intravenous infusion should be started, typically at 20 mcg/min and titrated up every 3 to 4 minutes until the resolution of ischemia or the development of hypotension.²⁸

Nitrates should generally not be administered to patients who are markedly bradycardic, tachycardic, or hypotensive (systolic blood pressure below 90 mm Hg or a drop in blood pressure of greater than 30 mm Hg from their baseline).²⁸ Other contraindications include suspected right ventricular infarction, in which patients depend on their preload to maintain adequate blood pressure. Right ventricular (RV) infarction should be considered in every patient with an inferior wall myocardial infarction. Electrocardiographic evidence for RV infarction includes ST-segment elevation greater in lead III than in lead II and ST-segment elevation in V_1 or V_4R . An example is shown in Figure 16-8. Patients who have taken a phosphodiesterase inhibitor within 24 hours should not receive nitrates as well.²⁸ While the use of transdermal nitrates is commonplace, these preparations are of limited use in a patient with ACS due to the passive nature of administration. Active ACS in the ED or the ICU requires close monitoring and should be managed actively with periodic sublingual or continuous intravenous nitrates.

For many years, β -adrenergic blocking agents were commonly used in ACS patients to directly decrease cardiac work and oxygen demand based on early studies that showed a mortality benefit to patients who received intravenous agents on the day of their presentation.³⁰ More recent studies, however, have demonstrated increased morbidity with early β -blockade. The most dramatic results came from the COMMIT study that demonstrated increased risk of cardiogenic shock in patients receiving IV β -blockers within 24 hours of myocardial infarction.³¹ Based on this and similar studies, current treatment guidelines have limited their use to oral agents, started within 24 hours, for younger patients who do not have contraindications such as CHF, bronchospasm, cocaine abuse, low output states, heart block, and increased risk of cardiogenic shock.²⁸ Another recent review concluded that no evidence supports intravenous use of these agents over the oral route.³²

Morphine has frequently been used to provide analgesia for patients with anginal pain that is refractory to nitrates. Morphine is known to block catecholamine surge, resulting in decreased blood pressure, heart rate, and, consequently, oxygen demand.²⁸ It is also postulated to play a role in preventing further plaque rupture.²⁸ This potentially beneficial action has not been demonstrated in the literature, however. In fact, one observational study demonstrated an increased likelihood of death in ACS patients receiving morphine, possibly related to masking of ongoing cardiac ischemia.³³ Despite this concern, the ACC and AHA have continued to support the judicious use of morphine as the analgesic agent of choice for refractory pain despite maximal treatment with other anti-ischemic medications.

Antiplatelet Therapy

Aspirin is an irreversible COX-1 inhibitor that minimizes platelet activation and aggregation by blocking arachidonic

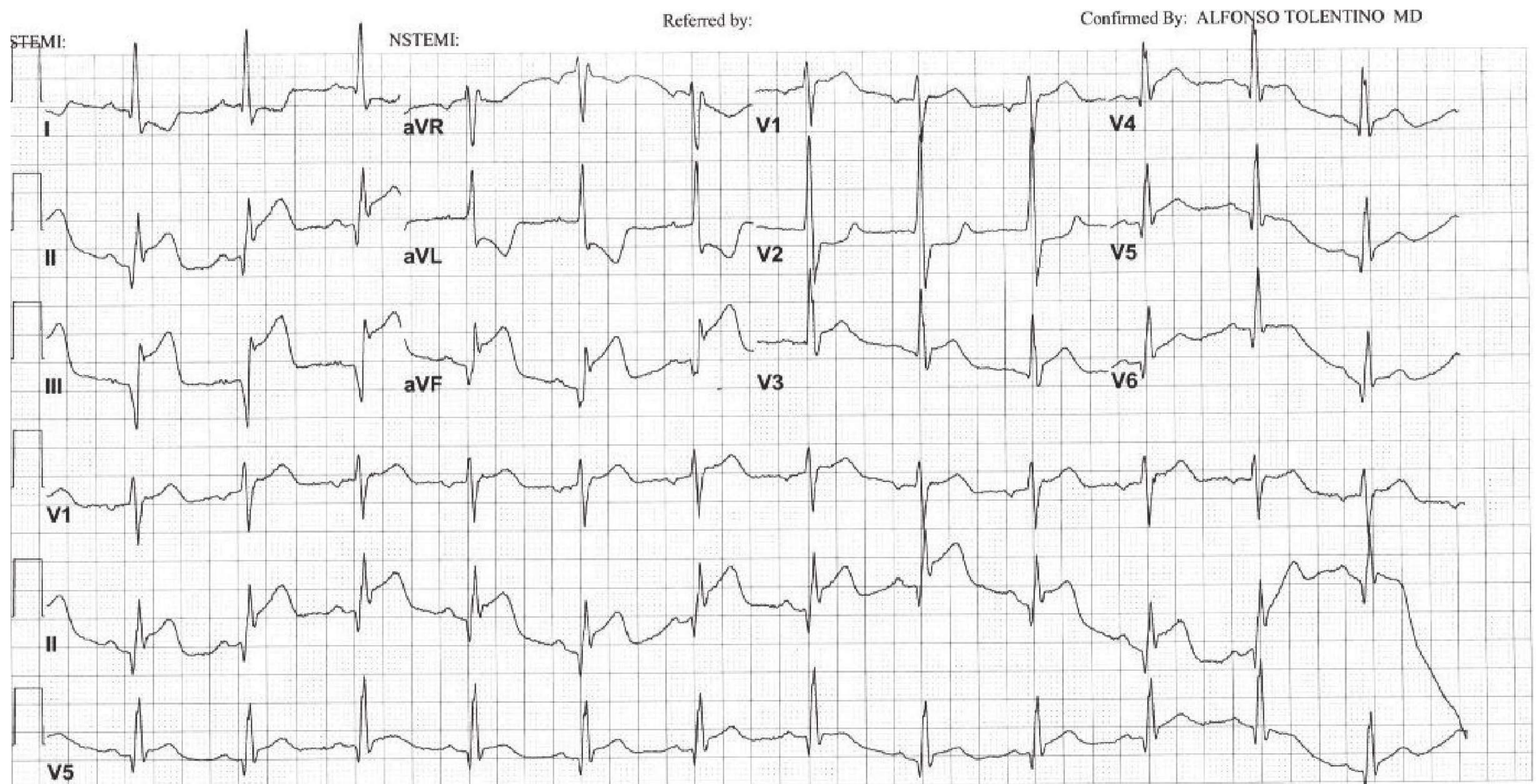
acid. This prevents further clotting in ACS and was shown to reduce mortality in the ISIS-2 study at doses of 162 mg.³⁴ The utility of aspirin was further confirmed in two subsequent meta-analyses.^{35,36} The common practice of chewing aspirin, rather than swallowing the pills whole, has been demonstrated to deactivate platelets more quickly.^{37,38} Current recommendations are for 162 to 325 mg of aspirin to be given immediately after the onset of symptoms, in the prehospital setting if possible, or on arrival to the hospital.²⁸ Aspirin should be avoided in patients with allergy or significant active bleeding or bleeding risk.²⁸

Clopidogrel is a thienopyridine that also inhibits platelets irreversibly by antagonizing the adenosine diphosphate receptor. It has been shown to be equally effective for ACS in patients who cannot receive aspirin and should be given to these patients in place of aspirin for suspected ACS.³⁹ Some papers have recommended a 600-mg loading dose in these patients, as opposed to a 300-mg loading dose for patients who will also receive aspirin.⁴⁰ Its utility in ACS, when combined with aspirin, was demonstrated in the CRUSADE and CURE trials that both showed modest improvements in survival with dual antiplatelet therapy despite a small increase in bleeding complications.^{41,42} Other studies demonstrated dual antiplatelet benefit for patients less than 75 years old with STEMI who undergo thrombolysis or for whom no revascularization treatment is planned.^{43,44} Based on these findings, ACS patients who do not have PCI planned within 48 hours should receive clopidogrel 300 mg or ticagrelor 180 mg early in their hospital course in addition to aspirin.²⁸

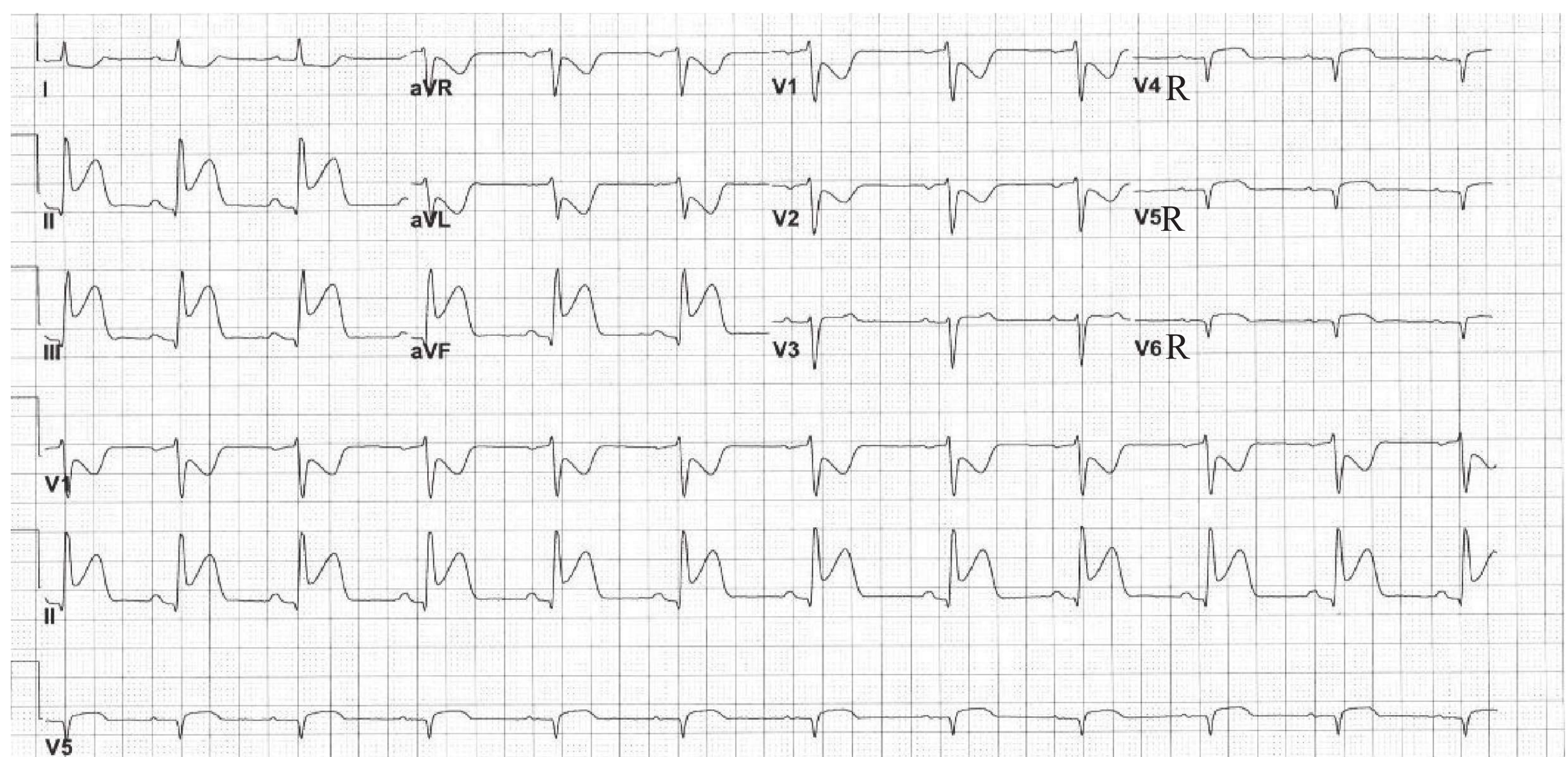
For patients with STEMI or planned early PCI, the use of thienopyridines is less well established but data has been growing. It may still be used as an aspirin substitute, as described earlier, but there is some controversy regarding dual antiplatelet therapy in these patients. The early supporting literature on this treatment strategy demonstrated some benefit but was a somewhat flawed subgroup analysis of a larger study.⁴⁵ The use in PCI patients is further complicated by the fact that both the CURE and CRUSADE trials demonstrated additional bleeding complications for patients with dual antiplatelet therapy who underwent CABG within 5 days of administration of clopidogrel.^{41,42} However, neither of these studies demonstrated an increased mortality in these patients. Since most patients do not undergo CABG within 5 days of PCI, the most recent recommendation is to administer 600 mg of clopidogrel or 180 mg of ticagrelor to all STEMI or ACS patients undergoing PCI.^{28,46}

While the current STEMI guideline still includes 60 mg of prasugrel, a recent large study has cast doubt on its pre-PCI utility in NSTEMI patients.⁷⁰ It should be noted that prasugrel has some caveats when compared with clopidogrel: if possible, CABG should be delayed for 7 days after the last prasugrel dose and it should not be used in patients who have a history of stroke or transient ischemic attack.⁴⁶

The final category of antiplatelet agents, glycoprotein IIb/IIIa inhibitors (GPI), block fibrinogen cross-linking of activated platelets and consequently prevent platelet aggregation. There are two general types of GPIs: large-molecule, such as



A



B

FIGURE 16-8 **A.** Inferior wall myocardial infarction with ST elevation in II, III, and aVF. ST elevation in III > ST elevation in II suggestive of a right ventricular infarction. **B.** Right sided chest leads in the setting of an inferior wall myocardial infarction, reveals ST-segment elevation in V4R, V5R, and V6R suggestive a right coronary artery involvement affecting the right ventricular infarction. (Used with permission from Alfonso O. Tolentino MD.)

abciximab, and small-molecule, such as eptifibatide, and tirofiban. The largest body of data is on abciximab, which has been shown to be beneficial in patients undergoing PCI for STEMI.^{47,48} Similar evidence exists for small-molecule GPIs, eptifibatide and tirofiban.^{49,50} The small-molecule GPIs are

also recommended as part of an early invasive strategy for ACS without STEMI.²⁸ The evidence for GPIs in patients with ACS who undergo a conservative management strategy without planned PCI demonstrated increased complications without significant benefit.⁵¹ Therefore, the current recommendation

restricts GPI use to patients at the time of catheterization as part of a double or triple antiplatelet strategy.⁴⁶ These agents are typically continued in the ICU for up to 24 hours after the time of presentation.

Anticoagulant Therapy

The commonly used anticoagulants, unfractionated heparin (UFH), low-molecular-weight heparin (LMWH), and the newer fondaparinux, function by activating the enzyme anti-thrombin III that in turn inactivates thrombin and factor Xa, thereby inhibiting the clotting cascade. UFH is a naturally occurring substance that contains molecules of a variety of lengths. This is relevant because the longer heparin molecules inactivate both factor Xa and thrombin, while the shorter molecules inactivate only factor Xa. LMWHs, such as enoxaparin or dalteparin, are formulations of heparin containing primarily short-chain heparin molecules, and consequently inhibit factor Xa to a much greater degree than thrombin. Fondaparinux is a short-chain, synthetic, heparin-like molecule that functions like LMWH but only inhibits factor Xa.

Because their activity is more focused, these three can be dosed subcutaneously in a more predictable manner and do not require monitoring, unlike UFH, which requires a continuous infusion and monitoring of partial thromboplastin time (PTT). Because LMWH and fondaparinux do not affect thrombin, neither medication results in alteration of PTT. Similarly, LMWH is much less likely to produce heparin-induced thrombocytopenia (HIT) and fondaparinux has no risk of HIT. Consequently, both can be used for an extended period without significant risk of developing HIT, although patients with a history of HIT should preferentially receive fondaparinux.

The data on these medications in ACS are complex, with multiple competing studies producing somewhat conflicted results. Trials of UFH added to aspirin failed to show significant benefit in multiple small studies, but showed some benefit when analyzed together.⁵² In contrast, the LMWHs have been shown to be directly beneficial in ACS when added to aspirin.⁵³ Comparisons between LMWH and UFH have been mixed, with some showing benefit for LMWH and others showing no difference between LMWH or UFH.^{54–56} These studies have been performed in patients receiving both conservative management and early invasive management with PCI.⁵⁷ Of note, some of these studies demonstrated an apparent increased risk of bleeding associated with LMWH, although some analysis indicates this may have been due to switching between the two medications.⁵⁸ A rational regimen should ensure that the initial anticoagulant given for ACS be continued throughout the patient's hospital stay, assuming no contraindication develops, such as HIT.

In contrast, fondaparinux has a lower rate of bleeding complications than either UFH or LMWH and has been demonstrated to be equivalent to LMWH for ACS-NSTEMI patients when directly compared or even superior in one large registry study.^{59,60} As a result of these data, it is currently considered a first-line option for anticoagulation in ACS patients

although it is not recommended as the sole anticoagulant for STEMI.^{28,46}

The bottom line, however, is that these medications are essentially equivalent for NSTEMI, and local culture, rather than empiric evidence, will likely play a larger role in medication selection. LMWH may carry a slightly higher bleeding risk. LMWH and fondaparinux may provide some benefit over UFH when patients are treated for longer than 48 hours due to the increased incidence of HIT after 2 days of UFH. UFH is preferred for STEMI and when CABG is planned within 24 hours due to its more rapid clearance.⁴⁶

Bivalirudin is a newer anticoagulant and functions by direct thrombin inhibition without any anti-factor Xa activity. It is derived from hirudin, a natural anticoagulant produced by leeches. It is administered as a drip, has a very rapid onset of action, and reverses very quickly when stopped. Bivalirudin also carries no risk of HIT and has produced the lowest rates of bleeding complications of any of the anticoagulants, although the literature is limited in its use for ACS. One large study demonstrated benefit in patients undergoing PCI, but was complicated by the use of other medications.⁶¹ Bivalirudin is currently recommended as a treatment adjunct in STEMI and ACS patients undergoing PCI but is best administered in consultation with the treating cardiology service.⁴⁶

Reperfusion Therapy

The initial decision to reperfuse a patient with ACS should be based on the ECG. Frank STEMI indicates complete occlusion of a coronary artery and requires acute intervention. The choice of reperfusion strategies for STEMI patients is highly dependent on local resources. The general rule is that the timeliness of reperfusion is more important than the manner in which it is achieved. Assuming equivalent availability of both approaches, PCI provides superior outcome compared with intravenous thrombolysis.^{62,63} However, for patients who cannot receive PCI within 2 hours, there is no difference between the two modalities. Therefore, thrombolytics should not be delayed for PCI unless the PCI can be accomplished within 120 minutes of first medical contact.⁴⁶

Thrombolytics are more widely available than PCI and have been demonstrated to produce good outcomes in STEMI patients when administered in a timely fashion. However, the quality of the outcomes worsens as time to treatment lengthens. Whenever possible, the “door to needle” time, the interval between ED arrival and initiation of IV thrombolytics, should be less than 30 minutes for any STEMI patient with less than 12 hours of symptoms.⁶⁴ The currently used medications for thrombolysis are alteplase, reteplase, and tenecteplase, which are all tissue plasminogen activators. While the dosing of these medications differs widely, the reperfusion and complication rates are similar and most institutions have only one of the three available. Streptokinase, which is an older thrombolytic, has generally fallen out of common use given its worse side effect profile. There are clearly defined contraindications to the administration of thrombolytics and these are listed in Table 16-5.⁴⁶


TABLE 16-5: Contraindications to the Administration of Fibrinolytics
Absolute contraindications

Prior intracranial hemorrhage	Significant head trauma within 3 months
Known structural cerebral vascular lesion	Suspected aortic dissection
Known malignant intracranial neoplasm	Active bleeding
Ischemic stroke (CVA) within 3 months	Bleeding diathesis

Relative contraindications

Chronic severe hypertension (HTN)	Ischemic CVA greater than 3 months ago
Uncontrolled HTN (SBP > 180, DBP > 110)	Dementia
Prolonged CPR > 10 min	Other intracranial pathology
Internal bleeding within 2–4 weeks	Active peptic ulcer
Noncompressible vascular puncture	Current anticoagulant use
Pregnancy	

Data from O’Gara PT, Kushner FG, Ascheim DD, et al: 2013 ACCF/AHA guideline for the management of ST-elevation myocardial infarction: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines, *Circulation*. 2013 Jan 29;127(4):e362–e425.

Primary PCI is the treatment of choice for STEMI if it can be accomplished in a timely fashion. While the goal for PCI in the STEMI patient had traditionally been to achieve a “door to balloon” time (the time between arrival and the inflation of the balloon during angioplasty) of 90 minutes or less, this number has been replaced in the newest STEMI guidelines. The updated recommendation is that systems of care, starting with first medical contact in the field, should be designed to minimize the amount of time to diagnose STEMI, activate the cardiology team, and transfer the patient to the catheterization lab in order to ensure device deployment within 120 minutes of first medical contact. For STEMI patients presenting to facilities without PCI availability, transfer to a PCI-capable institution should be initiated immediately if the patient can be transferred and treated within the 120-minute window.⁴⁶

There are three additional, nonprimary forms of PCI that can be considered in the STEMI patient. Rescue PCI should be considered within 24 hours if a patient does not have an acceptable response to primary thrombolytic therapy as evidenced by less than 50% resolution of ST-segment elevation within 90 minutes, persistent unstable arrhythmias, persistent ischemic symptoms, or development or worsening of cardiogenic shock. Facilitated PCI is a strategy involving planned PCI after less than full-dose thrombolytics in a patient with high mortality risk when PCI is not available within 120 minutes. Follow-up PCI is common after primary fibrinolysis and considered after primary PCI if there

is evidence of persistent narrowing of coronary arteries that may be amenable to further intervention.⁴⁶

It should be noted that, as a system, hospitals may have reached a point of diminishing return when it comes to speeding reperfusion after first medical contact. A very large retrospective study of 96,738 patients demonstrated no change in mortality despite improving door to balloon time from 88 minutes to 68 minutes. The implication of this research is that further efforts to improve mortality in STEMI patients should be directed at other aspects of care such as improving patient awareness of symptoms, speeding 911 activation and improving post-discharge care.⁶⁵

Patients with NSTEMI or ACS patients without myocardial infarction generally have only partial occlusion of the coronary vessels and the benefits of early reperfusion therapy are less clear. Classically, these patients have been managed conservatively with medication followed by risk stratification, such as treadmill testing, but without reperfusion therapy. Some of these patients may also undergo diagnostic PCI, with the opportunity for stenting concerning lesions, as part of their initial hospitalization. Investigations of thrombolysis in these patients have demonstrated no benefit and a trend toward harm.⁶⁶ PCI within 48 hours, however, may confer some benefit to the ACS patient as demonstrated in a *Cochrane* systematic review of the literature and a meta-analysis, particularly for patients at high risk for recurrent events.^{67,68} A different meta-analysis showed a benefit for early PCI in patients with positive biomarkers, but no benefit in men with negative biomarkers, and a detrimental effect in women with negative biomarkers. Regardless of the initial choice of management, patients with high-risk features as described earlier or those with refractory or recurrent ischemia should receive early PCI and dual anti-platelet therapy assuming the patient does not have substantial comorbidities.²⁸

POTENTIAL COMPLICATIONS

The complications associated with ACS are clearly not just related to those of the cardiovascular system, but for the purpose of this discussion we will mention only those deemed most significant and related directly to the cardiovascular tree. A few of those mentioned are discussed in other sections of this book.

All types of derangements in electrical conduction may be encountered: those that have little to no effect on prognosis, such as sinus bradycardia, first-degree AV block, second-degree AV block type I, premature atrial contractions, and premature ventricular contractions, and those that have a significant impact on patient outcome, such as persistent sinus tachycardia, supraventricular tachycardia, atrial fibrillation, atrial flutter, and both right and left bundle branch blocks. With respect to ventricular tachycardia and fibrillation, the presence of either of these rhythm disturbances does not portend a poor prognosis early in the course of an acute myocardial infarction. In contrast, ventricular tachycardia or fibrillation that is delayed in its onset and encountered later in the course of disease is typically due to transmural infarction and severe ventricular dysfunction and is therefore associated with a much more grave prognosis.



TABLE 16-6: Killip Clinical Classification

Class	Approximate Mortality (%)
I: No congestive heart failure (CHF)	5
II: Mild CHF (bibasilar rales and an S3)	15–20
III: Frank pulmonary edema	40
IV: Cardiogenic shock	80

Reproduced with permission from Tintinalli JE, Kelen GD, Stapczynski JS: *Emergency Medicine: A Comprehensive Study Guide*, 7th edition. New York: McGraw-Hill Inc; 2011.

As mentioned earlier, BNP as a cardiac biomarker is utilized in such a way so as to risk stratify a patient with ACS.²⁸ Patients with CHF have a poorer prognosis than those without CHF. The clinical status of patients with CHF as defined by their Killip classification (Table 16-6) correlates with their percent mortality, with a higher classification indicative of a worse prognosis. For example, cardiogenic shock by itself or as a consequence of right ventricular infarction is defined as Killip Class IV and is associated with an approximate 80% likelihood of mortality, as opposed to those patients with no evidence of CHF (Killip Class I) who have an approximate 5% mortality.

A particularly lethal complication of myocardial infarction is ventricular free wall rupture that results in cardiac tamponade and death. Interventricular septum rupture may also occur, but the patient's ultimate prognosis depends on the size of the defect and the resultant degree of shunt created. Acute valvular insufficiency as a sign of papillary muscle rupture may be encountered and requires surgical correction.

Acute ascending aortic dissection, not as a consequence of but associated with acute myocardial infarction, is a rare occurrence but, when present, carries a high mortality. If unrecognized, 50% of patients will die within 48 hours. Most of these dissections involve the right coronary artery with coronary artery occlusion due to mural dissection or extravasation of blood into the pericardial space or perivascular tissues.

Other complications such as pericarditis with or without a pericardial effusion, ventricular thrombus formation with embolization, and postinfarct angina and extension are also possibilities.

DISPOSITION

Ascertaining the correct disposition for patients with ACS can be difficult. The disposition of patients with definitive evidence of disease is fairly easy. Patients who have undergone PCI or thrombolysis or with evidence of ongoing cardiac ischemia should be admitted to a cardiac intensive care unit. Many ACS patients, however, present with vague symptoms without electrocardiographic or laboratory evidence of disease. The disposition of this set of patients presents a challenge and can be highly dependent on local resources. Some EDs can provide early stress testing after repeat EKG and biomarker testing that may obviate the need for admission.

Other EDs offer chest pain units (CPU) with standardized pathways for monitoring and testing patients. After repeat lab testing, patients in CPUs frequently undergo risk stratification with stress testing, CT angiography, or catheterization depending on their findings and available resources.

In the ED, CPU, or on admission to the hospital, patients with suspected ACS should be observed with cardiac telemetry.²⁸ Given the volume of patients admitted for possible ACS and the relative paucity of telemetry beds, some researchers have attempted to develop decision rules regarding the need for telemetry monitoring. While these findings have yet to be included in the current guidelines, there have been some impressive results. One study evaluated the Goldman score, which was developed to assess perioperative cardiac risk, and found that it could reliably predict which patients could be safely admitted to an inpatient bed without telemetry monitoring.⁶⁹

Regardless of the ultimate disposition of ACS patients, current guidelines recommend that every patient undergo an evaluation of cardiac risk. This can be accomplished via exercise or chemical stress testing, radioisotope scanning, CT angiography, or cardiac MRI.⁷¹ A recent study and accompanying editorial suggest that there is no difference in outcomes between structural and functional testing.^{72,73} This should be accomplished during the initial ED visit or hospitalization. Low-risk patients can have this done as an outpatient, but arrangements should be made to ensure that it is accomplished within 72 hours of discharge.²⁸

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Hypertensive Crises

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INTRODUCTION

“The treatment of the hypertension itself is a difficult and almost hopeless task in the present state of our knowledge and in fact, for ought we know the hypertension may be an important compensatory mechanism which should not be tampered with even if it were certain that we could control it.”

Paul D. White, M.D., 1931, excerpt from “Cardiac Disease”

Hypertension is a common finding in patients presenting to the emergency department, and is seen in a broad range of conditions—from asymptomatic hypertension to acute intracranial hemorrhage. Determining the best management approach represents a significant challenge to emergency physicians and intensivists alike, and is a source of ongoing controversy. Essentially, three questions must be answered:

1. Will acute blood pressure reduction be helpful or harmful?
2. If blood pressure reduction is indicated, what is the target?
3. Which therapeutic agent should be used?

The diagnostic and therapeutic approach should not be algorithmic, guided strictly by numbers. Instead, clinicians should base their clinical decisions on a number of principles, most importantly the presence or absence of end-organ damage. Treat the patient, not the number.

EPIDEMIOLOGY

Hypertension is an increasingly important health care issue, with more than 50 million people in the United States having high blood pressure requiring treatment.¹ The prevalence increases with age, with more than half of people between the ages of 60 and 69 affected, increasing to more than three quarters of people over the age of 70.¹ Elevated blood pressure is noted in more than 25% of all patients presenting to the emergency department (ED).^{2,3} The ability to rapidly recognize and, when necessary, appropriately treat hypertension is therefore a critical skill for any practitioner in the emergency department (ED) or the intensive care unit (ICU).

DETERMINATION OF HYPERTENSION

Essential to appropriate management is first obtaining an accurate measurement. Ideally, patients should be seated with feet on the floor and arm supported at heart level. The auscultatory method should be used, and should be performed by a trained practitioner. The cuff bladder should encircle at least 80% of the arm, and at least two measurements should be performed with the average recorded. In reality, ED patients will often be screened utilizing automated BP cuffs against the backdrop of a chaotic waiting room or triage area, some of whom will still be strapped to an EMS gurney and *in extremis*. Take these measurements

with a grain of salt, and when in doubt, check the pressure yourself.

Arterial catheters are frequently recommended in place of noninvasive monitoring for patients on antihypertensive infusions, but there is surprisingly little evidence to support this position. A recent large cohort study evaluating the use of arterial catheters in critically ill patients in general requiring mechanical ventilation found no benefit on in-hospital mortality,³⁷ and there is at least some evidence that mean arterial pressure (MAP) measurements are similar between invasive and noninvasive approaches.³⁸ Arterial catheters can be a source of both infection and vascular compromise, and the decision to place an arterial catheter should be treated with the same prudence afforded to other invasive lines, like central venous catheters.

PATHOPHYSIOLOGY

Hypertension can be broadly divided into primary (“essential” or “idiopathic”) and secondary hypertension. Essential hypertension, so-named due to the belief that it was a compensatory mechanism that should not be interfered with, accounts for the majority of cases.⁴ Many causes have been hypothesized, but it is generally believed to be the result of renal mechanisms amplified by sympathetic nervous system activity and vascular remodeling.

Secondary hypertension can occur through a variety of causes. Renovascular disease, such as that due to renal artery stenosis or fibromuscular dysplasia, should be suspected in any young patient with hypertension or any patient with rapidly progressive symptoms. Decreased pressures in the lower extremities or delayed femoral pulses should raise the suspicion for coarctation of the aorta. Excessive glucocorticoids, resulting from either iatrogenic administration or endogenous overproduction, are also associated with hypertension. Physical signs and symptoms such as truncal obesity, glucose intolerance, and purple striae should suggest the diagnosis. Labile blood pressure with associated paroxysmal headaches, palpitations, pallor, and diaphoresis is the classic description of a pheochromocytoma.

CLASSIFICATION

The Eighth Report of the Joint National Committee (JNC) on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC 8), released in 2013, moved away from defining and classifying hypertension, and instead sought to focus on evidence-based treatment recommendations (though they grant that the JNC 7 definition of hypertension as 140/90 is still reasonable.)¹ Gone from the report is the controversial “prehypertension” diagnosis (120–139/80–89), along with dividing hypertension into “stage I” and “stage II” severity categories.

Acute severe elevations in blood pressure can be classified in a number of ways. Most commonly, practitioners consider hypertensive “emergency” to be uncontrolled hypertension in the setting of end-organ damage, particularly damage to

the renal, cerebral, or cardiovascular systems. There is general consensus on this definition. Hypertensive “urgency,” on the other hand, is murkily defined, and may not be effectively different than asymptomatic hypertension. Hypertensive urgency has previously been defined as severe acutely elevated BP without evidence of acute organ damage. What constitutes “severely elevated” varies among practitioners, but was previously defined by the JNC 7 as blood pressure greater than 180/120 mm Hg.

The distinction between hypertensive emergency and urgency/asymptomatic hypertension is critical as it dictates the timing and goals of blood pressure reduction, the need for parenteral versus oral agents, and the appropriate disposition on leaving the ED.

HYPERTENSIVE URGENCY AND ASYMPTOMATIC HYPERTENSION

The majority of patients presenting to the ED with hypertensive urgency have previously diagnosed hypertension and most often present in the setting of various painful symptoms.⁵ The level of hypertension necessitating treatment, and the choice of agent used, varies among practitioners.⁵ However, most would agree that, in the absence of end-organ damage, blood pressure should not be normalized in the ED but instead should be controlled over a period of several days through the use of oral agents.³³

The treatment strategy in the ED should begin with attempts to alleviate pain and anxiety, including providing patients with a quiet room if possible. These interventions alone may decrease the blood pressure to acceptable levels. If the patients are already being treated for hypertension, their home blood pressure medications should be given if they have not already taken them that day. If they have been compliant with their home medications, an increase in dosage can be considered or an additional agent added to their home regimen, although this should ideally be done in coordination with their primary physician.

If a decrease in blood pressure is desired over a period of hours to acceptable levels in the ED, oral agents such as clonidine (0.1–0.3 mg) or captopril (12.5–25 mg) may be given. Discharge home may be considered if the patient can be relied upon to closely follow up with his or her primary doctor within the next several days and no other compelling reason exists to admit to the hospital. All patients should be counseled on lifestyle modifications including weight loss, dietary sodium restriction, and regular aerobic activity.

HYPERTENSIVE EMERGENCY

Hypertensive emergency is generally defined as uncontrolled hypertension in the setting of end-organ damage, and treatment with titratable intravenous (IV) agents should be instituted immediately. The choice of agent and the goals of therapy should be based on the specific clinical presentation and are summarized in Table 17-1.

 **TABLE 17-1: Medication Options for Hypertensive Crises**

End-Organ Dysfunction	Recommended Agents
Encephalopathy	Nitroprusside, labetalol, fenoldopam, nicardipine
Stroke	Labetalol, nicardipine, nitroprusside
Acute myocardial ischemia	Nitroglycerin, esmolol, metoprolol
Acute pulmonary edema (suspected systolic dysfunction)	Nitroglycerin, ACE inhibitor, nitroprusside, fenoldopam (in combination with a loop diuretic)
Acute pulmonary edema (suspected diastolic dysfunction)	Nitroglycerin, esmolol, labetalol, metoprolol (in combination with a loop diuretic)
Aortic dissection	Labetalol, or esmolol with nitroprusside or nicardipine
Hypertension of pregnancy (preeclampsia or eclampsia)	Labetalol, nicardipine, hydralazine (consider magnesium sulfate)
Renal failure	Nitroprusside, labetalol

ACE: angiotensin-converting enzyme.

Critical to the management of any hypertensive emergency is the concept of autoregulation. Autoregulation is the ability of an organ to maintain a near-constant blood flow despite variations in perfusion pressure. The autoregulatory response is intrinsic to the specific organ’s vascular bed, and is independent of neural or humoral factors. Although examples of autoregulation can be seen throughout the body, it is most prominent in the cerebral, coronary, and renal vascular beds. However, autoregulation is only maintained over a certain range of perfusion pressures. Outside of this range, changes in blood pressure are directly reflected in the microvasculature. This leads to ischemia in the setting of hypotension, and hyperperfusion injury in the setting of hypertension. Additionally, chronic hypertension can cause this autoregulatory range to be shifted to a higher range of pressures. Attempting to rapidly normalize elevated blood pressures in such patients may in fact lead to hypoperfusion and ischemia.

SPECIFIC CONDITIONS

Hypertensive Encephalopathy

Under normal conditions, cerebral perfusion is maintained relatively stable over a wide range of blood pressures, due to the ability of the brain to autoregulate its blood flow. Hypertensive encephalopathy results from a cerebral perfusion pressure above this level of autoregulation, and represents a true medical emergency. The precise pathophysiology of hypertensive encephalopathy is not completely understood. With sudden elevations of blood pressure, the ability of the brain to autoregulate its

blood flow is lost, resulting in vasodilation, breakdown of the blood–brain barrier and cerebral edema. It has been linked to the reversible posterior leukoencephalopathy syndrome (RPLS), also known as posterior reversible encephalopathy syndrome (PRES),⁷ in which acute elevations in blood pressure lead to white matter edema mostly in the posterior parietal–temporal–occipital regions of the brain. In both conditions, symptoms can be rapidly reversed with appropriate and timely lowering of blood pressure. However, if inadequately treated, these symptoms can progress to cerebral hemorrhage, coma, and death.⁶ No exact value of blood pressure is pathognomonic for hypertensive encephalopathy, although cerebral autoregulation can be overwhelmed at MAPs as low as 120 mm Hg in previously normotensive individuals.⁶ However, individuals with chronic hypertension often have autoregulatory curves that have been shifted to higher pressures, and may not develop symptoms of hypertensive encephalopathy until MAPs have exceeded 150 mm Hg or higher. Clinically, hypertensive encephalopathy is manifested by symptoms of headache, nausea, lethargy, altered mental status, and seizures. When associated with the RPLS, symptoms may also include visual abnormalities, including cortical blindness, homonymous hemianopsia, and blurred vision.⁷ On physical exam, signs of increased intracranial pressure (ICP) such as papilledema may be seen. Focal neurologic deficits are generally not found on exam, although they may occur if hemorrhage or infarction occurs. The differential diagnosis is wide and includes intracerebral hemorrhage, brain tumor, meningoencephalitis, toxidromes, and cerebrovascular accident (CVA). Hypertensive encephalopathy represents a true medical emergency, and efforts at blood pressure reduction should begin immediately when this is suspected. An initial goal blood pressure reduction of 20% to 25% is generally advised, or a goal diastolic of 100–110 mm Hg. A titratable agent should be used, such as nicardipine, esmolol, or labetalol.

Ischemic Stroke

Antihypertensive therapy in the setting of stroke remains an area of considerable controversy. In these scenarios, hypertension may represent both a contributing factor and a physiologic response to the stroke syndrome. Despite the widespread prevalence of stroke syndromes, an optimal treatment strategy regarding blood pressure management has not been established.^{8,9} Elevated blood pressures have been shown to be a prognostic indicator of stroke mortality, with observational data suggesting that SBP exceeding 180 mm Hg in the ED is associated with a 5-fold risk of poor neurologic outcomes.⁹ It is unclear, however, whether this is a causal relationship or merely a correlate of stroke severity. In the setting of ischemic stroke, there are several theoretical reasons why antihypertensive therapy would be beneficial. Lowering blood pressure could reduce edema around the damaged area, decrease the risk of hemorrhagic transformation, and lessen further vascular damage.

However, aggressive treatment of hypertension in the setting of ischemic stroke could also reduce perfusion in ischemic areas, thwarting the brain's compensatory mechanisms. This risk of causing harm, combined with the lack of data supporting benefit, suggests that aggressive lowering of blood pressure should be avoided in the acute phase of stroke.

The American Heart Association and American Stroke Association have offered guidelines⁸ for the management of hypertension in the setting of ischemic stroke, most recently updated in 2013. The consensus is to withhold treatment unless the hypertension is severe, defined by this council as systolic > 220 mm Hg or diastolic > 120 mm Hg. The recommendation in these scenarios is to reduce blood pressure by 15% *in the first 24 hours* after stroke onset, with labetalol and nicardipine being the preferred agents.

These recommendations change for those patients who are candidates for thrombolytic therapy. In these patients, elevated blood pressures represent an increased danger of intracerebral hemorrhage and should thus be controlled. Blood pressure should be lowered to < 185 mm Hg systolic and < 110 mm Hg diastolic prior to administration of a thrombolytic agent, and should be maintained below these levels for 16 hours after therapy.⁸ Again, labetalol boluses and nicardipine infusion are the recommended agents, although nitroprusside may be necessary in refractory cases.

In most cases of ischemic stroke, elevated blood pressures decrease spontaneously without treatment. Additional measures to lower ICP, such as raising the head of the bed, and measures to reduce pain and anxiety can also lower blood pressure through non-pharmacologic means.

Hemorrhagic Stroke

For hemorrhagic stroke, representing approximately 15% of all strokes, the optimal treatment strategy is equally controversial.^{9,11–13} Hypertension in the setting of intracranial hemorrhage is often severe due to increased ICPs and irritation of the autonomic nervous system. Similar concerns exist for initiating therapy including the balance between decreasing the risk of further bleeding and hemorrhagic enlargement, with the concern for decreasing cerebral perfusion pressure.

Current guidelines for patients with intracerebral hemorrhage, released in 2010 from the American Heart Association/American Stroke Association,¹² recommend reducing the systolic pressure to 160 mm Hg if the pressure is greater than 180 mm Hg. Alternatively, a systolic pressure target of 140 mm Hg is considered safe if the presenting systolic pressure is less than 220 mm Hg. If systolic pressure is above 220 mm Hg, reducing the pressure to less than 160 mm Hg is not recommended.¹² The ongoing ATACH-II trial, randomizing patients to a systolic target of either < 140 mm Hg or < 180 mm Hg, will seek to add clarity to this issue.

In the case of aneurysmal subarachnoid hemorrhage, general recommendations are to maintain the systolic blood pressure below 160 mm Hg,¹³ though the evidence is modest, and neurosurgeon preference may be to maintain pressures < 140 mm Hg. Pain control, sedation, and ICP-lowering

measures, such as raising the head of the bed, should be instituted prior to administering antihypertensive agents. The use of oral nimodipine to prevent delayed cerebral vasospasm will also have a modest hypotensive effect.

As with ischemic stroke, when the decision is made to lower blood pressure, the agents used should be rapid acting and easily titratable, such as nicardipine, labetalol, or esmolol. Blood pressure monitoring should be continuous, via arterial line monitoring, or at short and regular intervals for noninvasive cuff pressures.¹²

Congestive Heart Failure

Congestive heart failure (CHF) represents a clinical syndrome of inadequate cardiac output with a resulting cascade of events, including catecholamine surge, increased peripheral vascular resistance, increased intravascular and interstitial volumes, and varying degrees of pulmonary edema. The hypertension associated with CHF can be both a cause and effect of this process, and needs to be lowered rapidly to relieve symptoms and improve clinical outcome. Nitroglycerin is generally the first-line agent, given by continuous infusion, with initial doses of 50 to 100 mcg/min that can be increased to 200 to 400 mcg/min if needed. (If these doses seem high, consider that three sublingual nitroglycerine tablets over 15 minutes at 0.6 mg/tab is equivalent to a 120 mcg/min infusion.) Nitroglycerin should be rapidly titrated downward upon patient improvement.

Angiotensin-converting enzyme (ACE) inhibitors such as captopril or, if unable to tolerate PO, enalapril or enalaprilat may be helpful. Diuretics, such as furosemide, should be used to reduce fluid overload and improve work of breathing, recognizing that their benefit will be primarily in the subacute and stabilized phase. Although β -blockers are widely used in patients with chronic CHF, they are generally avoided in acutely decompensated states due to the negative inotropic and chronotropic effects.

Additional measures, including supplemental oxygen, BiPAP, and even mechanical ventilation, are often necessary. With an improvement in respiratory status, the catecholamine surge is often relieved, subsequently lowering blood pressure and breaking the pathologic cycle.

Cardiac Ischemia

Myocardial ischemia or infarction associated with hypertension warrants immediate blood pressure-lowering therapy to minimize myocardial damage. Agents of choice include nitroglycerin and IV β -blockers such as metoprolol, in some select cases. ACE inhibitors are also an important part of the therapy in the setting of an acute coronary syndrome; however, care should be taken to avoid overshoot hypotension when co-administered with nitroglycerin and β -blockers. Evidence from the PROVE IT-TIMI trial suggests that there is no benefit beyond lowering blood pressure to the 130–140/80–90 range, with possible harm induced by bringing pressures < 110/70.³⁶

Renal Failure

Hypertension can be seen as both a cause and effect of renal failure. Renal disease leads to hypertension both through increased salt retention and through activation of the renin–angiotensin system. Additionally, uncontrolled hypertension may cause acute kidney injury and can accelerate the progression of injury in patients with chronic renal failure. Worsening kidney function in the setting of elevated blood pressures should be considered a hypertensive emergency and warrants treatment.

Nitroprusside is considered a first-line agent for hypertension-induced acute renal failure, although labetalol is often preferred due to the decreased risk of overshoot hypotension. ACE inhibitors, although highly effective in controlling chronic renal disease, should be used cautiously in the setting of acute renal failure as they may worsen the process acutely.

Emergent dialysis may be indicated in patients with end-stage renal disease with acute uncontrolled hypertension in the setting of volume overload or any evidence of other end-organ dysfunction.

Pregnancy

Hypertensive disorders complicate between 6% and 8% of all pregnancies¹⁴ and represent a significant source of morbidity and mortality to both the mother and the fetus. Up to 15% of maternal deaths in the United States are attributable to hypertensive disorders, making it the second leading cause of maternal mortality after thromboembolic disease.¹⁴

Classification of pregnancy-associated hypertensive disorders is based on the level of blood pressure elevation, the presence of proteinuria, and physical signs and symptoms. Hypertension in pregnancy is defined as a systolic blood pressure ≥ 140 mm Hg or a diastolic pressure ≥ 90 mm Hg. The level of hypertension is classified as severe if the systolic blood pressure is ≥ 160 mm Hg or the diastolic pressure is ≥ 105 –110 mm Hg.¹⁵ Hypertension in pregnancy occurring prior to 20 weeks' gestation is termed *chronic hypertension*, most likely antedating pregnancy. Hypertension occurring after 20 weeks, but without proteinuria or any signs or symptoms, is termed *gestational hypertension*. *Preeclampsia* is defined as hypertension occurring after 20 weeks with proteinuria (> 300 mg in 24 hours) or other clinical or laboratory abnormalities. *Eclampsia* refers to the occurrence of seizures or coma in the presence of preeclampsia.

Severe preeclampsia or eclampsia, or pregnancy-associated hypertension with any signs or symptoms indicative of end-organ damage, represent true hypertensive emergencies and should be treated emergently. Treatment goals in the ED should include blood pressure reduction, seizure prevention and control, and early obstetric consultation.

The specific goals of blood pressure reduction are not well defined. Severe, acute elevations in blood pressure can be associated with cerebral and cardiovascular complications, as well as placental abruption and uteroplacental insufficiency.¹⁵ However, some evidence suggests a parallel between reduction in MAP and adverse effects on fetal growth.¹⁶ Some

advocate withholding treatment unless diastolic blood pressure remains persistently elevated above 105 to 110 mm Hg.¹⁴

Hydralazine had previously been the frontline agent of choice, although this has come into question in recent years.¹⁵ It is still widely used and is an effective agent, though caution must be taken due to its unpredictable dose–response curve. Labetalol is now the drug of choice for pregnancy-associated hypertensive emergencies.¹⁷ Nicardipine may also be effective, although there has been some concern about administering it in patients also receiving magnesium sulfate for seizure prophylaxis, due to the combined calcium channel–blocking activity.¹⁵ Nitroprusside should be reserved to severe hypertension refractory to other agents, due to the potential for fetal cyanide toxicity and overshoot hypotension. ACE inhibitors are contraindicated in pregnancy, as they may induce fetal renal damage.

Aortic Dissection

Aortic dissection should be suspected in any patients presenting with chest pain that is sharp or “tearing” in quality, radiates to the back, and is maximal at onset. However, up to 20% may present with syncope without a history of typical pain or other findings.¹⁸ Physical exam findings pointing to a diagnosis of aortic dissection include pulse deficits, a diastolic murmur, and neurologic deficits (due to dissections that extend to the common carotid arteries). A high index of suspicion should always be maintained, as inappropriately treating for a presumed acute coronary syndrome or stroke could be devastating for patients with aortic dissection.

Aortic dissection represents a hypertensive emergency in which the treatment approach is two-pronged. Since propagation is dependent on both the level of hypertension and the left ventricular ejection force, therapy must be aimed at both lowering pressure and slowing the rate of pressure rise. Generally, a β -blocker such as esmolol is used, often in combination with a vasodilator such as nitroprusside. Alternatively, labetalol, which has both α - and β -blocking effects, can be used as monotherapy.¹⁹ Goal blood pressure should be 100 to 120 mm Hg systolic.

All patients with suspected aortic dissection require prompt surgical consultation. However, aneurysms involving only the descending aorta (Stanford type B) are generally medically managed.

PHARMACOLOGY

The agents used to treat hypertensive urgency, as described in the earlier sections, will now be considered individually. Parenteral agents are summarized in Table 17-2.

Antiadrenergics

LABETALOL

Labetalol is a combined α_1 -blocker and nonselective β -blocker. The ratio of α - to β -blockade is 1:7 in the IV form.²³ As a result, labetalol is an effective blood pressure–lowering agent that has the advantage of not causing reflex tachycardia.



TABLE 17-2: Dosage and Effects of Common Parenteral Agents in Hypertensive Emergency

Medication	Dosage	Onset	Duration	Adverse Effects	Comments
Nitroprusside	0.3 µg/kg/min, titrate to maximum 10 µg/kg/min	Seconds	1–2 min	Cyanide toxicity, flushing, nausea, vomiting, headache, lactic acidosis	Avoid in setting of increased cerebral pressure or pregnancy Monitor for cyanide toxicity with prolonged use
Esmolol	Loading dose: 500 µg/kg over 1 min Infusion: 25 µg/kg/min, titrate to maximum 200 µg/kg/min	5–10 min	20 min	Bradycardia, nausea, flushing, bronchospasm	Avoid in acute heart failure with systolic dysfunction
Labetolol	Bolus: 20 mg initially with repeat doses of 20–80 mg Infusion: 1–2 mg/min to maximum 24 h total of 300 mg	5–10 min	6–8 h	Nausea, vomiting, bronchospasm, bradycardia, orthostatic hypotension	Avoid in acute heart failure with systolic dysfunction
Nicardipine	5 mg/h, increase by 2.5 mg/h every 5 min to maximum of 15 mg/h	5–10 min	4–6 h	Headache, nausea, flushing, reflex tachycardia	Use with caution in patients with liver failure
Nitroglycerin	5 µg/min, titrate by 5 µg/kg every 5 min to maximum 200 µg/min	Seconds	3–5 min	Headache, dizziness, tachyphylaxis	Use with caution in patients with right heart failure
Fenoldopam	0.1 µg/kg/min, titrate by 0.1 µg/kg/min every 15 min to maximum 1.6 µg/kg/min	10–15 min	30–60 min	Flushing, tachycardia, headache, nausea, vomiting	Use with caution in patients with asthma or glaucoma
Hydralazine	5–10 mg initially, repeat doses of 10 mg every 15 minutes	5–15 min	12 h	Tachycardia, headache, nausea, orthostatic hypotension	Effect may be unpredictable. Avoid in setting of myocardial ischemia or aortic dissection
Phentolamine	1–5 mg bolus 50 µg/min, titrate to maximum 500 µg/min	1–5 min	15–30 min	Flushing, reflex tachycardia, nausea, vomiting, hypotension	Used for catecholamine-induced state such as cocaine toxicity and pheochromocytoma Avoid in myocardial ischemia

When given IV, onset of action is 5 to 10 minutes with a high volume of distribution and duration of action of approximately 6 to 8 hours. Dosing is usually begun at 20 mg IV for hypertensive emergencies with repeated doses of 20, 40, or 80 mg every 5 to 10 minutes until desired blood pressure is reached, up to a maximum of 300 mg. Alternatively, a continuous infusion of 1 to 2 mg/min can be initiated after the initial bolus dose.

When goal blood pressure is reached, transition to oral form can be initiated. Orally dosing is generally begun at 200 mg. Onset of effects with oral dosing is approximately 1 to 3 hours.

Labetalol has little effect on cerebral or coronary blood flow and can be used safely in patients with acute myocardial infarction. Due to its β -blockade effect, use with caution in patients with decompensated heart failure or in acute exacerbation of asthma or chronic obstructive pulmonary disease (COPD). It should also be avoided in patients with cardiac conduction system abnormalities. In low doses intravenously, due to the high ratio of β to α effects, there is a theoretical risk of paradoxical hypertension with administration to patients in

high catecholamine-induced hypertension, such as that seen with pheochromocytoma or cocaine-induced hypertension.

ESMOLOL

Esmolol is a selective β_1 -antagonist with an ultrashort half-life of approximately 9 minutes. It is easily titratable, due to its short duration of action of approximately 10 to 20 minutes. Esmolol is metabolized by red blood cell esterases, making it additionally useful in patients with hepatic and renal failure.²⁴

Infusion is generally begun with a bolus of 250 to 500 mcg/kg over 1 minute, followed by an initial infusion of 25 mcg/kg/min. This can then be titrated up by increments of 25 to 50 mcg/kg/min every 4 minutes until goal blood pressure, or heart rate, is reached or to a maximum of 300 mcg/kg/min.

Adverse effects may include bradycardia, hypotension, dizziness, somnolence, nausea, and bronchospasm. As with all β -blockers, use with caution in patients with CHF, asthma,

COPD, heart block, and bradycardia, or in the setting of cocaine overdose or pheochromocytoma.

CLONIDINE

Clonidine is a centrally acting α_2 -agonist that lowers blood pressure through negative feedback on the vasomotor center of the brain, decreasing sympathetic discharge. It is an oral agent, and can be effective in cases of hypertensive urgency when blood pressure reduction is desired over a period of hours. Onset of action is between 30 minutes and 2 hours, with a duration of action of 6 to 8 hours. Dosing is begun at 0.1 to 0.2 mg orally, with additional doses 0.1 mg given hourly as necessary until goal blood pressure is reached. Side effects include sedation and dry mouth, and clonidine may sometimes cause orthostatic hypotension.³²

PHENTOLAMINE

Phentolamine is an α -adrenergic blocking agent most useful in management of catecholamine-induced hypertensive emergencies. It is generally given as 5-mg boluses, with an onset of action within 1 to 2 minutes and a duration of action of 10 to 30 minutes. It is contraindicated in the setting of myocardial ischemia, except when associated with cocaine toxicity, and may cause reflex tachycardia and tachydysrhythmias as a side effect. It is also injected subcutaneously in the setting of vasopressor infiltration, to prevent local tissue necrosis.

Calcium Channel Blockers

NICARDIPINE

Nicardipine is a parenteral calcium channel blocker of the dihydropyridine class. It acts as a powerful vasodilator, but, unlike other calcium channel blockers such as nifedipine, it has the advantage of lacking significant negative inotropic effects.²⁵ It has become a front-line agent for controlling blood pressure in the setting of intracranial and subarachnoid hemorrhage.

Nicardipine is generally begun at a rate of 5 mg/h and titrated every 5 minutes to a maximum of 15 mg/h or until the desired blood pressure is reached. Onset of action is within minutes, and duration of action is 4 to 6 hours.

Headache is a common side effect, occurring in up to 20% to 50% of patients.²⁶ Less commonly, tachycardia, nausea, and overshoot hypotension are seen. Caution should be used in patients with liver failure, as it is heavily metabolized by the liver.²⁷

CLEVIDIPINE

Clevidipine is an ultrashort acting IV calcium channel blocker that was approved by the FDA in 2008 for the treatment of severe hypertension. It is easily titratable, with blood pressure reduction seen within 2 to 3 minutes of administration and a duration of action of 5 to 15 minutes.^{29–31} Additionally, since it is cleared by plasma esterases, it requires no dosage adjustment for patients with hepatic or renal impairment. Dosing is begun at 1 to 2 mg/h and titrated up

until desired blood pressure is reached. Titration is generally performed initially by doubling the dose every 90 seconds, although this titration should be done every 5 to 10 minutes if the blood pressure is near goal. A maximum of 16 mg/h is recommended; however, limited data exist for dosages up to 32 mg/h.^{29–31} Adverse effects include headache, nausea, and chest discomfort.

Nitrodilators

NITROGLYCERINE

Nitroglycerin is a rapidly acting vasodilator that lowers blood pressure in a dose-dependent fashion. It primarily acts on the venous system, thus decreasing preload more than afterload. It is therefore most useful in cardiac ischemia or heart failure associated with hypertension. Initial dosages may vary widely between 5 to 100 mcg/min, depending on whether it is being used for cardiac ischemia (lower doses) versus acute pulmonary edema (higher doses). The primary side effects of nitroglycerin are headache and tachycardia. It should be avoided in the setting of right heart failure, as a precipitous drop in cardiac output and blood pressure may result.

SODIUM NITROPRUSSIDE

Nitroprusside is an extremely powerful and effective pressure-lowering agent, acting as a potent vasodilator in both the arterial and venous systems. Due to its rapid onset of action (1–2 minutes), short half-life (3–4 minutes), and almost universal effectiveness, it was widely considered the standard drug of choice in hypertensive emergencies. However, due to its high potency, overshoot hypotension is a common complication. Close hemodynamic monitoring, preferably with an intra-arterial line, is required. Infusion of sodium nitroprusside is generally begun at 0.3 mcg/kg/min and titrated up to goal MAP, with a maximum dose of 10 mcg/kg/min.²⁰

Sodium nitroprusside is metabolized by the liver to thiocyanate that is then excreted by the kidneys. Cyanide is an intermediate metabolite in this process, although cyanide toxicity is rare. However, thiocyanate toxicity may occur in the setting of hepatic or renal failure or prolonged administration.²⁰ Use of this agent is also complicated by the need for special handling, as it is unstable in the presence of ultraviolet light and must be wrapped in opaque material during administration. Caution should be used in patients in whom increased cerebral pressure is a concern, as nitroprusside acts as a cerebral vasodilator. Additionally, nitroprusside should be avoided in pregnant patients due to its ability to cross the placenta and cause cyanide toxicity in the fetus.

ACE Inhibitors

CAPTOPRIL

Captopril is an oral ACE inhibitor that, like clonidine, can be useful in situations of hypertensive urgency, in which a more gradual blood pressure reduction is desired. Dosing is 12.5 to 25 mg with an onset of action between 15 and 30 minutes,

and a duration of action of 4 to 6 hours. Side effects may include cough or skin rash. A more rare, but serious, side effect to ACE inhibitor therapy is angioedema, which may be life-threatening. ACE inhibitors are contraindicated in pregnancy.

ENALAPRILAT

Enalaprilat is an IV ACE inhibitor that has been shown to be effective at lowering blood pressure without causing overshoot hypotension.³⁴ It is the active metabolite of the oral ACE inhibitor enalapril. Dosing is generally begun with a dose of between 0.625 and 1.25 mg IV. Peak effects occur within 10 to 15 minutes with a duration of action of 12 to 24 hours. Adverse effects may include renal failure, angioneurotic edema, and cough. ACE inhibitors are contraindicated in pregnancy.²⁸

OTHER AGENTS

Hydralazine

Hydralazine is a direct arterial vasodilator, commonly used in pregnancy-induced hypertension. Onset of action is approximately 10 minutes when given intravenously with a duration of action of 4 to 6 hours. However, the effects can often be unpredictable, with an initial 5- to 15-minute latent period followed by an often precipitous drop in blood pressure, which may last up to 12 hours.^{22,25} Doses are generally begun at 5 to 10 mg IV, with repeated doses of 10 mg every 10 to 15 minutes until goal blood pressure is reached. Reflex tachycardia is a common complication, and thus should be avoided in patients with myocardial ischemia or aortic dissection. Other adverse effects include headache, nausea, and postural hypotension. Chronic use may lead to a lupuslike syndrome.

Fenoldopam

Fenoldopam mesylate is a selective postsynaptic dopamine-1 receptor agonist that functions both as a systemic and renal vasodilator and as a natriuretic. Like nitroprusside, fenoldopam has an onset of action within minutes and a short duration of action (less than 10 minutes). Additionally, it has been demonstrated to be as effective as nitroprusside in lowering blood pressure²¹ with less hypotension and no concerns of light sensitivity or thiocyanate or cyanide toxicity. For these reasons, fenoldopam is gaining favor by some as the drug of choice in treating hypertensive emergencies.

Fenoldopam is dosed initially at 0.1 mcg/kg/min and titrated in increments of 0.1 mcg/kg/min every 15 minutes until a desired pressure is reached. Side effects may include reflex tachycardia, headache, and facial flushing.

CONCLUSION

Hypertension, both symptomatic and asymptomatic, is commonly encountered in the ED in a variety of clinical contexts. The decision to treat, the target blood pressure, and the agent

used to attain it, all vary from patient to patient. Treating numbers is straightforward; treating patients is not.

One final emphasis: the terms “hypertensive emergency” and “hypertensive urgency” are used frequently in this chapter, but in reality, these are catchall terms that describe a wide array of illnesses. After all, no one refers to a patient having a “hypoxic emergency” or an “infectious emergency,” and so perhaps in the future we will abandon the term “hypertensive emergency” and talk more about specific clinical entities.

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Post-Cardiac Arrest Management

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INTRODUCTION

Sudden cardiac arrest is a leading cause of death in developed countries and impacts over 350,000 patients in the United States per year with an overall survival rate after out-of-hospital cardiac arrest of approximately 10%.^{1,2} Despite initial resuscitation, 50% of arrest victims do not survive to discharge from the hospital. One-third die from refractory cardiovascular shock or the cause of initial arrest. The remaining patients survive the initial insult only to later succumb due to organ dysfunction and neurologic injury stemming from the cardiac arrest. Among survivors, the burden of cardiac arrest persists, with up to 30% of patients suffering permanent neurologic injury. These data underscore the impressive health care burden of sudden cardiac arrest.

The early post-arrest period has emerged as a critical window to impact the outcome of cardiac arrest victims. Improved morbidity and mortality achieved with targeted temperature management (TTM) prove the potential for treatments applied following return of spontaneous circulation (ROSC) to impact clinical outcome. As such, contemporary emergency care now emphasizes intensive support during this vulnerable and modifiable phase of illness. Priorities of the post-arrest period include stabilization of organ perfusion and oxygenation, identification and treatment of reversible causes of cardiac arrest, and initiation of neuroprotective therapy (Table 18-1). This chapter focuses on the immediate and early post-resuscitation phase of illness, in which timely interventions provide the greatest opportunity to achieve the goal of neurologically intact survival of cardiac arrest victims.

THE POST-CARDIAC ARREST SYNDROME

Post-resuscitation disease is a unique multi-organ illness (Table 18-2).³ Reperfusion following a period of whole-body ischemia and hypoxia ignites a complex systemic immunologic response. Pro-inflammatory cytokines, coagulation abnormalities, and endothelial dysfunction characterize a state of systemic inflammation analogous to that of severe infection.⁴ The clinical consequence of this immune activation is macrocirculatory and microcirculatory dysfunction manifested as hemodynamic instability and early organ dysfunction.

Cardiovascular Dysfunction

Low and no-flow periods of cardiac arrest are invariably associated with global ischemia. However, adequate oxygen delivery is not restored with ROSC. A brief hyperdynamic cardiovascular response is common immediately following ROSC but is typically followed by early cardiovascular deterioration.^{5,6} The swiftness and degree of hemodynamic decline is inversely related to the period of cardiac arrest.⁷ Hypodynamic shock complicates more than half of cases in the first hours of care.⁸ As such, shock should be anticipated and represents an important target of therapy.

Post-ROSC shock is complex and multifactorial. Myocardial dysfunction stems from acute myocardial stunning, chronic disease, or the unresolved disease that incited cardiac arrest. However, primary cardiac dysfunction is rarely the sole lesion. The global cytokine storm and ischemic-reperfusion response following ROSC superimpose transcapillary leak

 **TABLE 18-1: Early Post-Resuscitation Priorities**

- Provide adequate oxygenation and ventilation
- Reverse shock and stabilize hemodynamics
- Identify and treat reversible cause of cardiac arrest
- Apply neuroprotective therapies including targeted temperature management
- Correct metabolic disturbances

and inappropriate vasoregulation to circulatory failure in the post-arrest period.

HEMODYNAMIC RESUSCITATION

Hemodynamic resuscitation is a cornerstone of critical care support. Guidelines endorse an early endpoint-driven resuscitation for hemodynamic optimization following ROSC.⁹ Early implementation of a structured hemodynamic optimization strategy improves survival in high-risk critical illness but is less rigorously studied in post-cardiac arrest syndrome.^{10,11} Standard hemodynamic manipulation focuses on preload optimization, blood pressure stabilization, and organ perfusion and oxygenation (Table 18-3). Post-resuscitation cardiovascular status is dynamic, making hemodynamic optimization an ongoing challenge. Invasive venous and arterial hemodynamic monitoring guidance should be strongly considered early in care.

Systemic arterial perfusion pressure is critical to maintain adequate organ blood flow. The brain is particularly vulnerable in the post-arrest period. Impairment of cerebral autoregulation exposes the brain to hypoperfusion even in the absence of systemic hypotension.¹² Early post-ROSC arterial hypotension affects more than half of patients and is associated with death and diminished functional status among survivors.^{5,13} As such, post-ROSC blood pressure represents an important target to improve outcomes and hypotension must be scrupulously avoided.

Inappropriate vasodilation contributes to hemodynamic instability early in post-arrest shock and should be corrected with catecholamine support simultaneous with volume

 **TABLE 18-2: Post-Cardiac Arrest Disease and Pathophysiology**

Systemic ischemia-reperfusion injury	Systemic inflammatory response syndrome (SIRS) Inappropriate vasodilation Impaired microvascular function Early organ dysfunction
Acute myocardial dysfunction	Myocardial stunning Acute coronary syndrome
Brain injury	Anoxic brain insult Ischemic reperfusion injury Impaired autoregulation
Persistent arrest precipitating pathology	

 **TABLE 18-3: Early Hemodynamic Resuscitation Goals Following Cardiac Arrest**

Resuscitation Priority	Monitor and Goal	Therapy
1. Preload optimization	Response to fluid challenge CVP 8–12 mm Hg Echo cardiac function and IVC variation Stroke volume variation	Fluid challenge
2. Perfusion pressure	MAP 65–100 mm Hg Strict avoidance of hypotension	Norepinephrine Vasopressin
3. Perfusion optimization	Global perfusion markers SvO ₂ > 65%/ScvO ₂ > 70% Lactate clearance and normalization Clinical perfusion markers Urine output (UOP) > 0.5 mL/kg/hr Peripheral skin perfusion	Dobutamine Milrinone IABP PRBC

resuscitation. Vasopressor requirement within the first hours of care is common, and delaying vasopressor support risks organ hypoperfusion. Norepinephrine is the preferred agent due to its potency, therapeutic dosing range, and side effect profile.¹⁴ A minimum mean arterial pressure (MAP) goal of 65 to 80 mm Hg is widely recommended.

The injured brain is especially vulnerable to hypoperfusion as cerebral autoregulation is impaired in the post-ROSC period with an absent or right-shifted autoregulatory range.¹² The optimal therapeutic arterial pressure and period of critical cerebral risk remain undefined. Spontaneous hypertension is associated with improved neurologic outcomes and should not be aggressively controlled in the absence of other end-organ dysfunction.¹⁵ MAP targets of 80 to 100 mm Hg may improve cerebral perfusion and have been incorporated into clinical practice.¹⁶ Special attention should be paid to the patient with chronic hypertension, which is a common comorbidity amongst post-arrest patients, as their baseline cerebral autoregulatory status may necessitate higher MAP to ensure adequate perfusion of all end-organs. Individual blood pressure goals should be balanced to avoid unnecessary afterload stress in patients with acute myocardial infarction or severe cardiomyopathy. Vasodilators, beta-blockers, and anti-dysrhythmics should be titrated judiciously given the high risk of post-resuscitation hypotension in this group.

Intravascular volume depletion, stemming from capillary leak and pathologic vasodilation, contributes to post-ROSC cardiovascular insufficiency. Restoration of oxygen delivery through fluid resuscitation relies on optimizing preload to maximize stroke volume. Total volume requirements are difficult to predict at the onset of resuscitation but are often underestimated. Crystalloid resuscitation totalling 50 to 80 mL/kg is typical in the first day of post-arrest support.^{17,18}

Cooled intravenous fluids serve the dual purposes of volume resuscitation and hypothermia induction.

The ultimate goal of resuscitation is to restore oxygen delivery and tissue perfusion to meet global and regional metabolic needs. Macrocirculatory signs provide little insight into the balance of systemic oxygen delivery and utilization.^{19,20} Resuscitation aimed to normalize traditional clinical targets of blood pressure, pulse, and central venous pressure (CVP) does not guarantee normal organ perfusion or resolution of oxygen delivery dependency, and therefore risks leaving the patient in persistent compensated shock.

Perfusion indicators are important markers of shock, and their normalization can be similarly targeted as endpoints of therapy during early resuscitation. Lactate clearance and central venous saturation (ScvO₂) are practical global markers of early resuscitation.^{21,22} Estimation of regional perfusion by clinical exam and urine output is also standard. Unfortunately, no single marker of resuscitation is perfect and a multimodal endpoint-driven resuscitation aiming to rapidly normalize all of several physiologic and laboratory variables is recommended (Table 18-3). Use of institutional protocolized order sets improves performance with resuscitation and is recommended.^{23,24}

Post-Cardiac Arrest Myocardial Dysfunction

Acute cardiac dysfunction independent of acute coronary occlusion is common following ROSC. Global systolic and diastolic stunning can be detected within minutes of ROSC but is not clinically relevant in all patients.²⁵ Severity varies, with cardiac function typically nadiring 6 to 8 hours post-ROSC.^{26,27}

Malperfusion despite preload optimization and blood pressure support often signals hypodynamic shock related to cardiac dysfunction and warrants consideration of inotropic or mechanical cardiac support. Despite sometimes severe dysfunction, myocardial stunning is responsive to therapy and frequently reversible within 48 to 72 hours.^{28,29} Inotropic support is required in up to 50% patients in some series.³⁰ Mechanical support in the form of intra-aortic balloon counterpulsation (IABP) or extracorporeal life support (ECLS) may also be required for severe or refractory cardiogenic shock.

PRECIPITATING PATHOLOGY

The acute precipitant of cardiac arrest must be considered as it may perpetuate shock and be amenable to specific therapy. Cardiac arrest represents the final common pathway of many lethal diseases, and prehospital data and records should be scrutinized to clarify premonitory signs and symptoms. Neurologic precipitants of cardiac arrest, including subarachnoid and intracerebral hemorrhage, should be considered before cooling, although neuroimaging is not mandatory for all patients.

Acute Coronary Syndrome

Heart disease remains the most common precipitant of sudden cardiac arrest in adults. The rate of acute coronary

occlusion is estimated at 30% to 50%.^{31,32} Revascularization is independently associated with survival and should be considered for all patients with strongly suspected acute coronary disease or ECG evidence of ST-elevation myocardial infarction (STEMI). Percutaneous coronary intervention (PCI) is the preferred method of revascularization. All cardiac arrest patients with STEMI are candidates for PCI and this should not be delayed due to an uncertain neurologic prognosis.³³ PCI can be safely performed concurrent with hypothermia and without door-to-balloon time delay, but efficient care requires multidisciplinary coordination.^{34,35}

Patient selection for emergent cardiac catheterization is notably challenging. Acute coronary occlusion is poorly predicted by clinical history and post-ROSC electrocardiogram findings.^{31,36} The incidence of acute coronary artery disease remains high even in absence of STEMI. Early cardiac catheterization is associated with improved survival in this group.³⁷ An early aggressive cardiac catheterization strategy is advocated when no clear alternative arrest etiology is present.

Thrombolysis is an acceptable reperfusion strategy for STEMI if PCI is not immediately available. Lysis does not appear to carry an untoward hemorrhage risk and is associated with improved survival and neurologic outcome.³⁸ Co-administration with therapeutic cooling has not been well investigated. Adjunctive aspirin and heparin are recommended for suspected or confirmed acute coronary syndrome. Acute β -blocker and ACE-inhibitor therapy should be withheld due to the high rate of hemodynamic instability in post-arrest patients.

Dysrhythmia Management

Cardiac dysrhythmia, principally ventricular tachycardia or fibrillation (VT/VF), is a common precipitating cause of cardiac arrest. Reversible conditions, including electrolyte disturbance and ischemia, should be considered. However, the role of antidysrhythmic therapy following ROSC from VT/VF arrest remains unclear, and prophylactic administration is not supported or recommended. A short course of therapy may be warranted for cases of recurrent malignant dysrhythmia or in patients who achieve ROSC in response to this therapy if no alternative reversible condition is identified.

Sinus bradycardia during therapeutic cooling is common and generally well tolerated. Negative chronotropes such as β -blockers and amiodarone should be avoided unless strongly indicated. Severe bradycardia complicating hypoperfusion during therapeutic cooling warrants elevation of the target temperature.

POST-ARREST CEREBRAL INJURY AND RESUSCITATION

Neurologic failure is the most common cause of death and disability among patients resuscitated from cardiac arrest. The brain is uniquely vulnerable to bioenergetic failure associated with ischemia during cardiac arrest. However, reperfusion triggers a secondary cascade, inciting cerebral injury that

evolves over hours to days.^{39,40} Neuroprotective drugs have not shown consistent promising results. However, therapeutic hypothermia trials established that therapies applied following ROSC are capable of modifying the secondary reperfusion insult and neurologic outcome.

Early prognostication of neurologic recovery among patients resuscitated from cardiac arrest is limited. Futile resuscitation efforts should not be pursued, but premature negative prognostication remains an obstacle to optimal care.⁴¹ Signs of neurologic function immediately following ROSC are encouraging, but their absence, including posturing and absent brainstem reflexes, does not preclude recovery. Neurologic prognosis of comatose patients cannot be reliably determined by arrest events, immediate post-resuscitation neurologic exam, or neuroimaging.^{42,43} Patient stabilization and initiation of neuroprotective therapies takes precedence over prognostication immediately following cardiac arrest. Accurate prediction of neurologic prognosis improves 72 hours after ROSC.⁴²

TARGETED TEMPERATURE MANAGEMENT

TTM is an integrated neuroprotective goal of post-arrest resuscitation. The mortality of patients who achieve ROSC remains high due to the neurologic consequences rather than the cause of cardiac arrest. TTM is the only neuroprotective therapy with clear neurologic and survival benefit following cardiac arrest.^{16,44,45} The landmark trials evaluated cooling in patients with a first recognized rhythm of VT/VF. Alternative rhythms were excluded to avoid experiment confounding. All other factors being equal, the brain and other organs suffer a similar injury regardless of the primary arrest rhythm or site of arrest (in or out-of-hospital). Observational experiences confirm the benefit of cooling for cases of non-VT/VF arrest.^{46,47} Guidelines support application of cooling for comatose cardiac arrest victims regardless of the initial rhythm or arrest precipitant. Serious hemodynamic instability and the need for emergency PCI and advanced cardiorespiratory support do not contraindicate cooling.⁴⁸

TTM strategies are evolving with new evidence. The initial landmark trials targeted 32 to 34°C. More recent evidence shows that TTM to 36°C provides comparable benefit.⁴⁹ While many centers continue to target the former goal, 36°C remains an option for patients that are intolerant or who have relative contraindications to lower temperatures. Regardless of goal temperature, active temperature control initiated at the onset of resuscitation cannot be neglected. Although generally well tolerated, therapeutic cooling is associated with some unique physiologic changes that should be recognized (Table 18-4).

The cascade of neuronal injury is accelerated with reperfusion. Temperature modulation of reperfusion injury is greatest when implemented early, and delays negate the beneficial impact.⁵⁰ Therapeutic cooling should be initiated as soon as possible following ROSC. While this has led to prehospital adoption of cooling, this does not obligate continued



TABLE 18-4: Potential Adverse Physiologic Responses and Complications Associated with Cooling

- Hypotension
 - Including vasodilation with rewarming
- Dysrhythmias
 - Sinus bradycardia during cooling is most common
- Cold diuresis
- Electrolyte abnormalities (K, Mg, Phos)
- Insulin resistance and hyperglycemia
- Coagulopathy and thrombocytopenia
- Infection (and under-recognition of signs of infection)
- Shivering
- Pancreatitis

therapy.⁵¹ On arrival to the hospital, patients should be individually evaluated for candidacy of cooling based on institutional guidelines and the potential risk and benefit of continued treatment. Patients with severe or terminal illness and those unlikely to survive an acute critical illness due to comorbid disease, irrespective of cardiac arrest, are poor candidates for cooling. Prolonged arrest intervals, including > 15 minutes to first resuscitation attempt or cardiac arrest longer than 40 minutes, are similarly associated with poor prognosis.⁵² The therapeutic window for cooling to provide benefit is unclear, but initiation of cooling should generally occur within 6 hours of ROSC.

Therapeutic cooling is practically divided into induction, maintenance, rewarming and normothermia phases (Table 18-5). Induction with ice-cold (4°C) isotonic fluid is safe, inexpensive, and effective.^{53,54} Application of ice packs to the neck, axilla, and groin augments induction and may be required for patients intolerant of volume loading. Automated, servo-controlled cooling devices are commonly deployed to facilitate temperature control. Core body temperature monitoring via bladder or esophageal sensor is recommended. Some new temperature-sensing urinary catheters sense bladder outlet temperature and do not require urinary flow.

Despite coma, hypnotic and opioid sedation should be employed for all patients to attenuate adrenergic response and shivering during cooling. Intermittent bolus or continuous neuromuscular blockade stops shivering and facilitates achieving rapid hypothermia. Thereafter, paralysis should only be used to combat refractory shivering that impacts maintenance temperature control. Intravenous magnesium and skin counter-warming are additional adjuncts for shivering control. External body surface or invasive cooling devices complete the induction phase and transition to maintenance temperature regulation. Cooling for 12 to 24 hours at goal temperature is recommended. Upon completion of the maintenance phase, slow and controllable rewarming at 0.3°C to 0.5°C/hour is recommended to avoid neurologic stress and hemodynamic and electrolyte changes. Continued temperature management with strict avoidance of hyperthermia is recommended for 48 hours.

**TABLE 18-5: Therapeutic Cooling Guidelines**

1. Perform and document neurologic exam
 - Eligible patient: GCS < 8 and/or no purposeful response to verbal commands
2. Hypothermia induction
 - Cooled intravenous fluids
 - 4°C 0.9% normal saline, 20–30 mL/kg bolus over 30 minutes as tolerated
 - Surface ice packs
 - Place core body temperature monitor (i.e., esophageal or bladder probe)
3. Shivering control
 - Early sedation and neuromuscular blockade
 - Midazolam 2–10 mg/hr
 - Propofol 20–50 mcg/kg/min
 - Fentanyl 50–150 mcg/hr
 - Vecuronium 0.1 mg/kg IV q45 minutes or as needed
 - Rocuronium 0.5 mg/kg IV q1 hour as needed
 - Cisatracurium 0.15 mg/kg bolus followed by 3 mcg/kg/min infusion
 - Adjuncts
 - Magnesium sulfate 5 g IV over 5 hours
 - Extremity skin counter-warming
4. Maintain goal 32–34°C for 12–24 hours
 - Recheck serum electrolytes and ABG upon reaching goal temperature
5. Rewarming
 - Slow controlled rewarming
 - 0.3–0.5°C/hr to 37.5°C
 - Stop sedation once temperature reaches 36.5°C
 - Maintain normothermia for 48 hours

Patients ineligible for therapeutic cooling warrant active measures to avoid post-ROSC hyperthermia. Fever is common after cardiac arrest and is associated with an unfavorable neurologic outcome.⁵⁵ Moderate to severe hypothermia associated with cardiac arrest warrants rewarming to the goal TTM range.

Post-Arrest Seizures

Seizures or myoclonus impact up to 30% of comatose survivors of cardiac arrest. Seizures in the post-arrest period have the potential to exacerbate cerebral injury and are associated with adverse neurologic outcome. However, post-arrest seizures and status epilepticus are not associated with uniformly poor outcome. Patients should be examined for evidence of seizure activity. Routine EEG monitoring would likely reveal subclinical non-convulsive seizures, but the timing of monitoring and impact of treatment remains unclear.⁵⁶ Standard seizure treatment with benzodiazepines, phenytoin, and barbiturates is recommended. Post-arrest myoclonus may be difficult to control, and clonazepam and levetiracetam are recommended therapies. There is no evidence to support prophylactic anticonvulsant therapy.

**TABLE 18-6: Acute Respiratory Management**

1. Lung-protective mechanical ventilation
 - Low tidal volume < 7 mL/kg (ideal body weight)
 - Plateau airway pressure < 30 cm H₂O
2. Avoid hyperventilation
 - Goals PaCO₂ 38–42 mm Hg
 - Hyperventilation (PaCO₂ < 35 mmHg) should not be used to compensate for metabolic acidosis unless severe (pH < 7.1)
3. Avoid hyperoxia
 - Rapidly titrate FiO₂ to SpO₂ > 95% (PaO₂ > 70 mm Hg)

Mechanical Ventilatory Support

Even in the absence of a precipitating respiratory disease, pulmonary complications, including respiratory failure, aspiration, and pneumothorax, are common in cardiac arrest victims. Prehospital extraglottic airway devices should be exchanged for a cuffed endotracheal tube upon patient stabilization to ensure airway protection. Adequate gas exchange and lung protection are the overriding principles of management for acute respiratory failure related to cardiac arrest (Table 18-6).

Inadvertent and purposeful hyperventilation is common with handheld resuscitation bags and contributes to auto-positive end-expiratory pressure (PEEP) with pulmonary and circulatory consequences.⁵⁷ Manual ventilation with a resuscitation bag should aim for single-handed ventilation (approximately 500 mL) and a normal respiratory rate and minute ventilation (rate 10–14). Lung-protective, low tidal volume, ventilatory support is likewise indicated on transition to the mechanical ventilator. Goal tidal volume is less than 7 cc/kg lean body weight and may require adjustment to lower tidal volumes depending on the degree of lung injury (see Chapter 4).

The metabolic conditions of post-ischemic organ blood flow (i.e., temperature, oxygen and carbon dioxide tension, pH, glucose) impact the secondary reperfusion insult. Mounting evidence points to supranormal tissue oxygen in the immediate post-resuscitation period as an avoidable accelerator of reperfusion injury and neuronal damage that impacts outcome.^{58,59} Hyperoxia can and should be avoided. Inspired oxygen concentration (FiO₂) should be rapidly titrated to physiologic levels (SpO₂ > 95%) following ROSC.⁶⁰

In contrast to cerebral autoregulation, cerebrovascular CO₂ reactivity is maintained in the post-arrest period. Hyperventilation risks cerebral vasoconstriction and hypoperfusion.⁴¹ Normocarbica is desired (goal PaCO₂ 38–42 mm Hg) with minimal adjustments recommended only for profound acidemia (pH < 7.1). Minute ventilation adjustments should be anticipated to maintain targeted normocapnia with reduced metabolism associated with therapeutic cooling.

Miscellaneous

Evidence-based supportive therapies for critical illness should be considered for all cardiac arrest patients (Table 18-7). Post-arrest patients suffer a significant rate of serious bacterial


TABLE 18-7: Evidence-Based Critical Care Support Therapies

1. Sterile barrier precautions for all invasive procedures
2. Safe mechanical ventilation
 - Low tidal volume < 7 cc/kg (ideal body weight)
 - Plateau airway pressure < 30 cm H₂O
 - Endotracheal tube (ETT) cuff pressure < 25 cm H₂O
3. Aspiration precautions for mechanically ventilated patients
 - Head of bed elevation > 30–45° unless contraindicated
 - Oro- or nasogastric tube decompression
 - Early antibiotic therapy for clinical evidence of aspiration
4. Blood sugar control; Goal BS < 180 mg/dL
5. Prophylaxis
 - Gastrointestinal stress ulcer prophylaxis
 - Deep venous thrombosis prophylaxis

infection.⁶¹ Nearly half of patients develop short-term pulmonary infection, likely a consequence of aspiration, which is associated with increased duration of mechanical ventilation and ICU stay.⁶² Although therapeutic cooling is not associated with increased infection risk, temperature control obscures a principal sign of infection and may delay early respiratory sampling and treatment. Early antibiotics are associated with improved outcome following cardiac arrest, and strict surveillance and low threshold for use is warranted given the high risk of this group.⁶³

Mixed metabolic and respiratory acidemia is common following ROSC. Cardiopulmonary support is the most important intervention to correct this condition. Extremes of blood glucose are associated with poor outcomes among post-arrest victims.^{64,65} Nondiabetic patients appear more susceptible. Arrest patients who are also at risk for hypoglycemia and blood glucose should be serially monitored during resuscitation. Current evidence supports targeting blood glucose less than 180 mg/dL via intermittent subcutaneous insulin or insulin infusion following initial patient stabilization.

Recognized complications associated with chest compressions and other resuscitation measures, including rib fractures, pneumothorax, pericardial effusion, and solid and hollow abdominal organ injury, should be considered.⁶⁶

CONCLUSION

The post-cardiac arrest patient suffers a complex systemic injury cascade that continues to evolve following ROSC. Timely interventions in the immediate and early

post-resuscitation phase are capable of modifying the natural trajectory of illness to achieve the goal of neurologically intact survival. Emergency care emphasizing critical care support, cardiovascular resuscitation, and neuroprotective cooling is a crucial link in the chain of survival (Table 18-8).

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TABLE 18-8: Avoidable Pitfalls in the Care of Post-Arrest Patients

- Failure to initiate early catecholamine support for BP stabilization
- Unnecessary hyperoxygenation
- Failure to provide revascularization therapy for patients with STEMI or strongly suspected ACS
- Delayed therapeutic cooling

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Vasopressors and Inotropes

Amber Rollstin • William C. Chiu • John P. Marshall

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A shock state is characterized by hypoperfusion to organs, cellular hypoxia, and metabolic disorder resulting in cellular injury. Injury to the organs is mainly due to the duration of the hypoperfusion and the speed with which the etiology can be treated and the shock state can be reversed. When patients are hemodynamically unstable, an important and potentially life-saving intervention is the use of vasoactive therapies to restore appropriate tissue perfusion by increasing blood flow and thereby increasing oxygen delivery. Prior to or concurrent with initiating vasoactive or inotropic medications, it is essential to attempt to identify the potential cause of the shock state and guide therapy based on this presumptive diagnosis. Refer to Chapter 61, Classification of Shock, for further information.

To review, mean arterial pressure (MAP) is the product of systemic vascular resistance (SVR) and cardiac output (CO). SVR is affected by blood viscosity, vessel length, and vessel diameter. The major determinant of SVR is the arterioles, which manipulate blood supply by dilating or contracting. CO is the product of stroke volume (SV) and heart rate (HR). SV is dependent on preload (end-diastolic volume), afterload, and cardiac contractility. Vasoactive therapies are used in an attempt to manipulate these important parameters and these relationships can be visualized using Formula 1. As demonstrated there, an increase in SVR, SV or HR will result an increase in MAP.

Formula 1: $MAP = SVR \times SV \times HR$

Vasoactive agents can be categorized by their activity and are often divided into two types: vasopressors and inotropes. The term “vasopressor” refers to a class of drugs that cause vasoconstriction. Typically, increasing vasoconstriction leads

to an increase in SVR, which leads to an increase in blood pressure. The term “inotrope” refers to a class of drugs that increase the strength of cardiac contraction. Increasing the strength of cardiac contractions will increase the stroke volume. By increasing SV, the intent is to increase the cardiac output (CO) and therefore increase blood pressure. Ultimately, the goal of either increasing SVR or increasing CO is to increase oxygen delivery to hypoperfused organs. Vasoactive drugs can also increase HR by increasing the sinoatrial conduction, giving them “chronotropic” properties. A “dromotropic” effect refers to an increase in atrioventricular (AV) nodal conduction.

Vasopressors and inotropic drugs can also be divided into two types based on their effects: adrenergic and non-adrenergic. The adrenergic agonists function at adrenergic receptors (α_1 , α_2 , β_1 , β_2) and dopaminergic (DA) receptors. The non-adrenergic agonists exert their effect primarily via the vasopressin-specific receptor (V_1 , V_2) or by inhibition of phosphodiesterase 3, which potentiates the effect of cyclic adenosine monophosphate (cAMP). It is crucial to have a good understanding of the physiologic function of these medications and their corresponding receptors, and to use this understanding to guide therapy. Table 19-1 provides a summary of the physiologic responses associated with each receptor.

RECEPTORS

α -Adrenergic Receptors

The main effect of α_1 stimulation is venous smooth muscle vasoconstriction. Agonism of α_2 causes vasodilation of the arteries and vasoconstriction of the veins; however, these


TABLE 19-1: Physiologic Actions of Receptors Stimulated by Vasopressors

Receptor	Physiologic Response
Dopamine (DA)	Vasodilation of major vascular beds (renal, coronary, cerebral, and splanchnic) and increased renal blood flow
β_1 cardiac	Inotropy and chronotropy
β_2	Peripheral vasodilation and bronchial smooth muscle dilation
α_1	Vasoconstriction
Vasopressin 1 (V_1)	Vasoconstriction
Vasopressin 2 (V_2)	Water retention

effects are negligible and often not considered clinically significant when compared with the α_1 effect.¹

β -Adrenergic Receptors

Agonism at the β_1 receptor produces an increase in cardiac contraction (inotropic), increased heart rate (chronotropic), and increased atrial conduction (dromotropic). β_2 stimulation causes relaxation of the smooth muscle of small coronary arteries and arteries of skeletal muscle resulting in vasodilation, as well as bronchiolar dilatation. There may be a chronotropic effect at higher dosages. β_3 receptors are mainly located in adipose tissue and may have some thermogenic effect.²

Dopaminergic Receptors

There are currently five recognized subtypes of DA receptors. Their main effect is to increase contractility, which results in an increased CO. Stimulation of these receptors can also result in an increased HR but this effect is dose dependent. There are also dopamine receptors in the kidney that produce diuresis and natriuresis.

SPECIFIC AGENTS

The vasopressors and inotropes that are most commonly used in the intensive care unit (ICU) are dopamine, dobutamine,


TABLE 19-3: Dosages of Common Vasopressors

Drug	Dose
Dopamine	Low dose: $< 5 \mu\text{g/kg/min}$ Moderate dose: $5\text{--}10 \mu\text{g/kg/min}$ High dose: $> 10 \mu\text{g/kg/min}$
Dobutamine	$2.0\text{--}20 \mu\text{g/kg/min}$
Epinephrine	For refractory hypotension Typical dosing is $1\text{--}4 \mu\text{g/min}$ ($1:10,000$ solution) For anaphylaxis, the dose and route change, based on the presence of shock: Without evidence of shock: $0.3\text{--}0.5 \text{ mg}$ ($300\text{--}500 \mu\text{g}$) IM q $5\text{--}10 \text{ min}$ ($1:1,000$) With evidence of shock: 0.1 mg ($100 \mu\text{g}$) IV, which is 1.0 mL of $1:10,000$ dilution IV given slowly over $3\text{--}5 \text{ min}$ or infused at $5\text{--}15 \mu\text{g/min}$
Norepinephrine	$0.03\text{--}3.0 \mu\text{g/kg/min}$
Vasopressin	0.04 U/min Not titrated
Phenylephrine	$0.5\text{--}8 \mu\text{g/kg/min}$ $100\text{--}180 \mu\text{g/min}$ IV drip
Isoproterenol	$2\text{--}10 \mu\text{g/min}$
Milrinone	$50 \mu\text{g/kg}$ bolus, then $0.25\text{--}1 \mu\text{g/kg/min}$

epinephrine, norepinephrine, vasopressin, and phenylephrine.³ Most vasoactive medications can cause serious complications when given through a peripheral IV (PIV), either by direct vasoconstrictive effect or via extravasation. It is recommended that these drugs be given via a central venous catheter. However, in emergent situations, these drugs can be given briefly through a PIV until a central venous catheter can be placed. Once these medications are started through a PIV, it should be a priority to obtain central venous access to minimize the time the drug is administered peripherally. A comparison of the hemodynamic effects of these agents is presented in Table 19-2, and typical dosing regimens are described in Table 19-3. It is important to recognize that dosing ranges can vary based on the reference being used and local hospital policies.


TABLE 19-2: Effect of Vasopressors on Hemodynamic Variables

Drug	MAP	SVR	HR	CO
Dopamine (moderate–high dose)	Increased	Increased	Increased	Increased
Dobutamine	Variable	Decreased		Increased
Epinephrine	Variable	Increased	Increased	Increased
Norepinephrine	Increased	Increased	$0 \rightarrow \text{decreased}$	Increased
Vasopressin	Increased	Increased		Increased
Phenylephrine	Increased	Increased	$0 \rightarrow \text{decreased}^a$	$0 \rightarrow \text{increased}$
Isoproterenol	Decreased	Decreased	Increased	Variable
Milrinone	Variable	Decreased		Increased

MAP, mean arterial pressure; SVR, systemic vascular resistance; HR, heart rate; CO, cardiac output.

^aPhenylephrine can produce reflex bradycardia as a side effect of hypertension.

Vasopressors

Norepinephrine is considered to be the initial vasopressor of choice. Norepinephrine is a strong agonist of α receptors and moderate agonist of β receptors, with greater β_1 action than β_2 . The effect is vasoconstriction greater than inotropy or chronotropy. This drug's effect on α receptors is increased with increasing doses. Norepinephrine increases left ventricular afterload, SV, and both systolic blood pressure (SBP) and diastolic blood pressure (DBP).

The indication for norepinephrine includes any hypotensive state despite fluid administration. It is common practice and acceptable to start a vasopressor during fluid therapy in the case of severe hypotension, with a plan to titrate the vasopressor off once the hypovolemia has been corrected. For many years, there was substantial debate as to whether norepinephrine or dopamine was the better initial vasopressor of choice. In 2010, a large, randomized controlled double-blind trial demonstrated the superiority of norepinephrine.⁴ Specifically, this trial demonstrated an increase in 28-day mortality among patients with cardiogenic shock who received dopamine as the first-line agent when compared to those who received norepinephrine alone. Also, the use of dopamine was associated with a greater number of adverse tachyarrhythmic events when compared to the norepinephrine group. As a result, this study has led to the recommendation that norepinephrine should be the initial vasopressor of choice for most shock states. The dose is 0.03 to 3.0 $\mu\text{g/kg/min}$. It is important to note that this medication is sometimes dosed in $\mu\text{g/min}$, rather than weight based. The dose for norepinephrine is then to start at 2 to 4 $\mu\text{g/min}$, with the usual dose at 2 to 30 mcg/min .

Side effects of norepinephrine include reflex bradycardia, HTN, arrhythmia, and dyspnea. Norepinephrine is contraindicated in patients with allergies to this medication class and should be used with caution in patients with severe allergies to sulfites. Hypovolemic states must first be treated with aggressive fluid therapy. Rare complication such as the risk of mesenteric or peripheral vascular thrombosis are present.

Dopamine is an immediate precursor of norepinephrine. It is an interesting drug in that it works on DA, β_1 , β_2 , and α_1 receptors at different doses. Dopamine increases contractility and HR by direct β -adrenergic action. It also indirectly stimulates norepinephrine release from nerves, and it is this action that makes the clinical prediction of its effects difficult.⁵ Dosage is based on ideal body weight. At *low dose* (1–2 $\mu\text{g/kg/min}$), dopamine acts on the DA receptors, and the effect is vasodilation of the renal, splanchnic, and mesenteric vasculatures. Some patients may become increasingly hypotensive at this dose. This is the dosage that, in the past, was termed “renal-dose dopamine” and was used to prevent acute renal failure (ARF). Several systematic reviews and one large randomized control trial concluded that dopamine did not prevent the onset of ARF. Nor did it shorten ICU or hospital length of stay, prevent the need for renal replacement therapy, or affect mortality.

Low-dose dopamine is no longer recommended for the prevention or treatment of ARF.⁶ At *moderate dose* (5–10 $\mu\text{g/kg/min}$), dopamine stimulates β receptors to a

greater degree than α receptors. The effect is inotropic and chronotropic but it also causes peripheral vasodilation. At *high dose* (> 10 $\mu\text{g/kg/min}$), dopamine causes an increased effect on the α receptors and less effect on the β receptors. Dopamine functions as more of a vasopressor at this dose. Because of the varying pharmacologic effects at different doses, dopamine is unpredictable and can be difficult to titrate. Providers must remain cognizant that with increasing doses of dopamine, the activated receptor profile changes.

The indications for dopamine as a first-line vasopressor should be reserved for patients who are hypotensive, refractory to fluid therapy and bradycardic with low inotropic activity. Dopamine's primary side effects include cardiac ectopy, tachycardia, angina, hypertension and dyspnea. Contraindications are limited to a true allergy, but it should be used with caution in patients with tachyarrhythmia or those with a reported allergic reaction to the sulfite preservative.

Epinephrine acts on all adrenergic receptors: α_1 , α_2 and β_1 , β_2 , and β_3 . Epinephrine, at low doses, will primarily have β effects, which will increase CO via β_1 receptors, making it a chronotrope and an inotrope. With increasing dosages, the α -adrenergic effect will become more prominent, causing increased total peripheral resistance in addition to an increased CO producing elevations of SBP and MAP. One of the main disadvantages of epinephrine is that it causes significant arrhythmia and splanchnic vasoconstriction, thus making it a second-line vasopressor in severe shock. Typical dosing varies depending on the clinical situation, and specific doses will be discussed under the specific indications to follow. It is also very important to be clear about the strength of solution—1:10,000 versus 1:1,000—when administering epinephrine for any condition. This distinction is further discussed in the section “Anaphylaxis.”

The indications for epinephrine include, but are not limited to, anaphylaxis, refractory hypotension, symptomatic bradycardia, severe exacerbation of asthma, and β -blocker overdose, particularly for patients in whom bradycardia is the predominant abnormality.⁷ For refractory hypotension, the typical dosing is 1 to 4 $\mu\text{g/min}$ (1:10,000 solution) given intravenously. For severe allergic reactions or anaphylaxis, the dose and route is adjusted based on the presence of shock, and will be discussed later in this chapter. Side effects of epinephrine include ventricular arrhythmia, hypertension (HTN), and cardiac ischemia. Caution should be used in patients with cerebrovascular insufficiency, heart disease, and angina. Push-dose usage of epinephrine is discussed in the section on transient hypotension to follow.

Vasopressin acts on V_1 receptors, which cause vasoconstriction, and V_2 receptors, which result in water retention. Vasopressin gained popularity as it was believed that vasopressin levels were either low normal or low in shock states. A randomized control trial of norepinephrine compared to norepinephrine plus vasopressin at 0.03 U/min demonstrated a favorable trend toward decreased mortality in patients for whom vasopressin was added to lower-dose norepinephrine (5–14 mcg/min). In contrast, vasopressin combined with a higher dose of norepinephrine demonstrated no mortality

benefit or outcome difference in septic shock patients.⁸ Vasopressin should only be used in situations in which other vasopressors are not enough to maintain the MAP at goal pressures. Vasopressin should never be the first-line vasopressor and should always be combined with other agents. The role of vasopressin in the treatment of other forms of vasodilatory shock has yet to be clearly defined.

The typical dosing of vasopressin is 0.03 to 0.04 U/min for the treatment of shock. This drug is not titrated. Side effects include cardiac ischemia, arrhythmias, mesenteric ischemia, and HTN. One advantage of vasopressin is that it maintains its effects in acidic and hypoxic environments, which are both typical in shock.²

Phenylephrine acts on α_1 receptors; the effect is primarily vasoconstriction at the venous and arteriolar levels, causing a significant increase in MAP without significant chronotropic or inotropic effect. Because it has little direct effect on the heart rate, there is minimal chance of developing an arrhythmia, but the blood pressure elevation can lead to a reflex bradycardia. It may be used as a primary agent in hypotension after spinal anesthesia or neurologic injury. It is also very useful in patients who require a vasopressor with minimal chronotropic effect such as those with underlying atrial fibrillation or other tachyarrhythmias. “Phenylephrine is not recommended in the treatment of septic shock except in circumstances where (a) norepinephrine is associated with serious arrhythmias, (b) cardiac output is known to be high and blood pressure persistently low or (c) as salvage therapy when combined inotrope/vasopressor drugs and low-dose vasopressin have failed to achieve MAP target.”⁹

Phenylephrine is initially started at 100 to 180 $\mu\text{g}/\text{min}$ via IV infusion for typically sized adults until SBP is stabilized. It is then reduced, if possible to 40 to 60 mcg/min . Phenylephrine is also sometimes utilized as a push-dose bolus, which is discussed in the section on transient hypotension to follow. Side effects include reflex bradycardia, HTN, and local necrosis in the event of extravasation.¹⁰

Contraindications to phenylephrine include hypersensitivity to sulfites. Phenylephrine should be used with caution in severe HTN, bradyarrhythmia and heart block, cerebrovascular insufficiency, and coronary artery disease (CAD) as it is associated with increased oxygen demand at the coronary arteries.

Inotropic Agents

Dobutamine is a potent β_1 receptor agonist and weak β_2 receptor agonist. Its effects are positive inotropy and chronotropy with slight peripheral vasodilation. Dobutamine usually causes an increase in CO. Dobutamine has very little effect on SBP; increases in SBP are seen in patients with cardiac dysfunction. SBP may drop in patients who are hypovolemic.

The indications for dobutamine include states with low CO or decompensated heart failure. Dobutamine is not recommended as a monotherapy in markedly symptomatic shock. For this situation, dobutamine is typically combined with norepinephrine or dopamine to provide peripheral

vasoconstriction and additional pressure support. Typical dosing of dobutamine is 2.0 to 20 $\mu\text{g}/\text{kg}/\text{min}$.

Side effects of dobutamine include tachycardia, hypertension, hypotension, ventricular ectopy, chest pain, dyspnea, and infusion site reactions. Contraindications include hypertrophic cardiomyopathy, history of malignant ventricular tachyarrhythmias, and sulfite sensitivity. Caution should be used with this drug when treating patients with SBP < 100 mm Hg.

Milrinone is a phosphodiesterase 3 inhibitor, which prevents the breakdown of cAMP, thereby simulating agonism at β_1 and β_2 receptors. Milrinone is often described as an “inodilator” because the effects are primarily inotropic, with significant vasodilation and less chronotropy. Due to the many side effects in hypotensive patients, milrinone and the newer generation of analogues have fallen out of favor as a drip and are more often dosed as a short-term intermittent infusion.¹¹ Typical dosing for milrinone is a 50 $\mu\text{g}/\text{kg}$ bolus, and then 0.25 to 1 $\mu\text{g}/\text{kg}/\text{min}$.

Side effects of milrinone include tachycardia, ischemia, hypotension, and thrombocytopenia. Contraindications include severe aortic or pulmonic obstruction and acute myocardial infarction (AMI). Use milrinone with caution in patients with atrial fibrillation or flutter, hypotension, hypertrophic subaortic stenosis, and renal impairment.

Isoproterenol is a β_1 and β_2 agonist, and has inotropic, chronotropic, and mild vasodilatory properties. The β_2 stimulation causes decreased DBP and MAP. Isoproterenol is rarely used; however, indications for isoproterenol include ventricular arrhythmias secondary to AV block, symptomatic bradycardia if pacing is not immediately available, and bradycardia after heart transplantation secondary to denervation.

Isoproterenol is no longer used as an inotropic agent in clinical practice because of its tendency to cause hypotension.¹² Typical dosing is 2 to 10 $\mu\text{g}/\text{min}$. Side effects include ventricular arrhythmias, cardiac ischemia, and HTN or hypotension. Contraindications to isoproterenol include digoxin toxicity, angina, cardiac arrhythmia, seizure disorder, renal insufficiency or failure, and CAD, and caution should be used when considering its use in elderly patients.

CLINICAL INDICATIONS

The choice of vasopressor is dependent on the clinical picture and the presumed etiology of the hypotension. Specific treatments based on clinical conditions are summarized in Table 19-4. The drug is then often titrated to achieve a desired endpoint. Examples of possible endpoints include, but are not limited to, CVP 8 to 12 mm Hg, MAP \geq 65 mm Hg, urine output \geq 0.5 mL/kg/h, venous (S_vO_2) or central venous ($S_{cv}O_2$) oxygen saturation \geq 70%, lactate clearance, and improved mental status.⁹ It is important to note that the optimal MAP for most conditions is unknown, but a post hoc analysis of a multicenter trial of septic shock demonstrated that elevations of the MAP > 70 mm Hg by augmenting the vasopressor dosage were associated with an increase in mortality.¹³ If the maximal dose of a drug is reached but not



TABLE 19-4: Treatment Based on Etiology of Shock

Shock Etiology	Initial Treatment	First-Line Agent	Second-Line Agent
Hypovolemic	Intravenous fluid (2 L of crystalloid)	Blood products as indicated or further intravenous crystalloid	<i>Norepinephrine</i> ^a <i>Dopamine</i> ^a <i>Epinephrine</i> ^a
Septic	Intravenous fluid (2 L of crystalloid)	<i>Norepinephrine</i>	<i>Dopamine</i> <i>Epinephrine</i> <i>Vasopressin</i> (if catecholamine resistant) <i>Phenylephrine</i> (combined with initial agent or alone if tolerated)
Anaphylactic	Intravenous fluid (2 L of crystalloid)	<i>Epinephrine</i> (IM if no shock)	<i>Epinephrine</i> (IV if in shock)
Neurogenic	Intravenous fluid (2 L of crystalloid)	<i>Norepinephrine</i> <i>Vasopressin</i>	<i>Phenylephrine</i> (monitor for reflex bradycardia)
Cardiogenic (right sided)	Intravenous fluid (20 mL/kg of crystalloid)	Vasopressors directed at cause of right heart failure <i>Dopamine</i> (with signs of shock) <i>Dobutamine</i> (without signs of shock)	Additional vasopressors as needed <i>Dopamine</i> <i>Epinephrine</i>
Cardiogenic (left sided)	Intravenous fluid as appropriate. Use caution in the setting of CHF	<i>Dobutamine</i> (without signs of shock) <i>Norepinephrine</i> (with signs of shock)	<i>Milrinone</i> (severe CHF or RV infarct) <i>Dobutamine</i> + <i>norepinephrine</i> <i>Epinephrine</i> (added to other agents) <i>Milrinone</i> (severe CHF or RV infarct)

IM, intramuscular; IV, intravenous; CHF, congestive heart failure; RV, right ventricle.
^aVasopressors should only be considered as a temporizing measure in extreme cases of hypovolemic shock while fluid resuscitation continues.

the desired endpoint, a second agent may be added. A critical care patient's hemodynamic status can change rapidly; therefore, it is important to frequently reevaluate the patient and determine if there is an ongoing need for vasopressor medication, titration, or a different agent. Excessive vasoconstriction can be detrimental, especially in the setting of inadequate CO and hypovolemia. When used in high doses without adequate volume or CO, these medications can lead to hypoperfusion of the kidneys, brain, and other organ systems.

While no studies have been done to definitively indicate that one vasopressor has improved mortality when compared with others when used for appropriate clinical conditions, the debate over dopamine and norepinephrine as the initial vasopressor of choice has been extensively studied. As discussed earlier, a large multicenter, randomized, blinded trial compared dopamine and norepinephrine as the initial vasopressor in the treatment of all patients presenting with shock regardless of etiology. This study concluded there was no mortality difference at 28 days when all forms of shock were examined.⁴ In the subset of patients with cardiogenic shock, however, dopamine was significantly associated with increased mortality. It also revealed that the use of dopamine was associated with a greater number of adverse events, such as arrhythmias, requiring medication discontinuation.⁴ It seems logical that norepinephrine should be the initial vasopressor of choice until further evidence suggests otherwise.

Prior to initiating vasopressors, it is important to ensure that the intravascular compartment has been repleted. In the case of distributive or hypovolemic shock, an adult patient should receive 2 L of crystalloid fluid before starting vasopressors. In cardiogenic shock, the patient should receive a

bolus of 20 mL/kg of crystalloid if there is right ventricular involvement. Fluid therapy is discussed at length in Chapter 57, Fluid Management. If the blood pressure fails to respond to these measures, vasopressors should be initiated. Vasopressor activity is partially, if not significantly, reduced if the patient has not been adequately volume resuscitated.¹⁴

Hypovolemic Shock

The treatment of hypovolemic shock is initiated with crystalloid fluids, with or without colloids. Vasopressors should generally not be used since they do not address the primary problem and may lead to further hypoperfusion. If the patient is in extremis, vasopressors should be used only as a temporizing measure in the setting of hypovolemic shock while fluid resuscitation continues. The cause of hypovolemia should be identified and treated, and it is essential to distinguish between hypovolemic shock and distributive shock, which is described in the next section. Transfusion should be considered early, particularly if the hypovolemic shock is due to blood loss. Fluid resuscitation should be continued, and the vasopressor agent should be weaned as soon as tolerated. Consider norepinephrine, dopamine, or epinephrine as a temporizing measure in this setting.

Distributive Shock

Distributive shock occurs when there is a fall in SVR secondary to significant peripheral vascular dilation. Causes of distributive shock include septic, anaphylactic, and neurogenic shock. Distributive shock is usually characterized by hypotension, low SVR, and normal to increased CO. Treatment

will be discussed in the next sections under the heading of each specific cause.

SEPTIC SHOCK

Septic shock may have both a distributive and cardiogenic component. Therefore, the initial goal of treatment is volume resuscitation followed by vasoactive infusions to increase SVR and increase CO. The first-line treatments of severe sepsis and septic shock are IV fluids (IVF) and antibiotics. If the patient remains hypotensive despite adequate volume resuscitation, then vasopressors should be added to the treatment regimen. Vasopressor therapy is important to improve and maintain adequate tissue perfusion in an attempt to maintain life and prevent the development of multiple organ dysfunction and failure.

The goal for initiating vasopressor therapy is a MAP of 65 mm Hg.⁹ There has been much controversy surrounding the initial vasopressor of choice in the management of patients with septic shock. For this reason, the Surviving Sepsis Campaign guidelines initially recommend either dopamine or norepinephrine as the initial vasopressor for patients with septic shock.⁹ However, these guidelines have changed in response to this study and other information. According to the Surviving Sepsis Guidelines 2013, norepinephrine is the first-choice vasopressor. Norepinephrine has both α activity to increase SVR and β adrenergic stimulation to augment CO. Epinephrine can be added to or may substitute for norepinephrine when a second agent is needed.

Vasopressin can be added to either further increase the MAP or attempt to decrease the norepinephrine dose. Vasopressin should not exceed the 0.3 to 0.4 U/min and should not be used as a first-line agent. Doses higher than 0.4 U/min should be reserved for situations in which there is a failure to achieve an adequate MAP despite the use of other agents. Dopamine is still discussed but as an alternative vasopressor in “highly selected” patient population such as those “patients with low risk of tachyarrhythmias and absolute or relative bradycardia.”⁹

The guidelines also recommend that phenylephrine not be used for septic shock unless the patient remains hypotensive despite the use of two or more vasoactive agents along with vasopressin. Phenylephrine is also acceptable when CO is known to be elevated or norepinephrine is thought to have caused a serious arrhythmia. A dobutamine trial is recommended for patients with septic shock who have low CO with high filling pressures on vasopressors or patients with evidence of hypoperfusion despite an adequate MAP and intravascular volume.

Epinephrine versus norepinephrine plus dobutamine was found to have no mortality benefit in a large prospective, multicenter, randomized double-blind European study.¹⁵

In a randomized double-blind study of septic shock patients requiring vasopressor therapy, there was no mortality difference between the norepinephrine and norepinephrine plus vasopressin group, but the combination of norepinephrine and vasopressin allowed for more rapid weaning of norepinephrine while maintaining adequate MAP.⁸

In the patient with a persistently depressed SvO₂ or ScvO₂ below 70% despite adequate blood pressure response to first-line vasopressor agents and after optimizing the hematocrit to a level above 30%, dobutamine can be added. In this setting, dobutamine can significantly increase cardiac index (CI), oxygen delivery (DO₂), and oxygen consumption (VO₂), while decreasing MAP, pulmonary artery and wedge pressures, and systemic and pulmonary vascular resistances. Hypovolemic patients have a poor response to dobutamine when compared with euvoletic patients, so it is essential to ensure adequate fluid resuscitation prior to starting dobutamine.^{16,17} Dobutamine should not be used as a first-line vasopressor for septic or other forms of distributive shock. Refer to Chapter 45, Sepsis and Septic Shock, for further information.

ANAPHYLAXIS

Anaphylaxis is a hypersensitivity reaction that involves all the components of the immune system, including immunoglobulin, cytokines, leukotrienes, prostaglandins, and activation of the complement cascade. The main culprit is histamine release, which causes capillary leak resulting in hypovolemia, bronchospasm, vasospasm, and mucous gland hypersecretion.¹⁸ The treatment of anaphylaxis should be guided by the need to prevent complications and reverse the inciting process. Special attention should be paid to securing the airway, and intubation, if indicated, should be done early. This should be followed by generous volume resuscitation, vasopressor support, and ultimately treating the histamine release.

Epinephrine is the vasopressor of choice and should be given early. Epinephrine dosage is something that is easily confused, and the literature contains a multitude of dosage variations, some in milliliters and others in milligrams or micrograms. Also, recommendations vary from country to country. First, it should be recalled that epinephrine concentrations vary. The commonly used terms, 1:1,000 and 1:10,000, are not completely obvious. Strictly speaking, these terms are structured as grams:milliliters of solution. Therefore, an epinephrine solution of 1:1,000 means 1 g of medication diluted in 1,000 mL (or 1 L) of solution. When each side of the ratio is divided by 1,000, the resulting amount is 1 mg/1 mL. This is obviously more concentrated than the 1:10,000 solution that has 1 g of medication diluted in 10,000 mL (or 10 L) of solution. In this case, dividing each side by 1,000 results in 1 mg/10 mL or 0.1 mg/1 mL. Epinephrine is packaged in a number of forms. Prefilled syringes, commonly used in cardiac arrest, come as 10 mL of 1:10,000 solution. As described earlier, this amounts to a total of 1 mg of epinephrine for the syringe at a concentration of 0.1 mg/mL.

The current clinical guideline for treatment of anaphylaxis recommends an initial epinephrine dose of 0.3 to 0.5 mg (or 300–500 μ g), which is the same as 0.3 to 0.5 mL of a 1:1,000 solution administered intramuscularly (IM) into the anterior or lateral thigh. Also, IM injection is recommended over subcutaneous (SQ) injection due to its more rapid increase in plasma and tissue concentrations of epinephrine.¹⁹ If shock is present or if symptoms are refractory to IM injection, then

the epinephrine should be given by continuous IV infusion at a rate of 5 to 15 $\mu\text{g}/\text{min}$. This can easily be done by mixing 1 mg of either solution into a 100-mL bag of normal saline, which produces a concentration of 10 $\mu\text{g}/\text{mL}$. This solution can then be run at 1 mL/min, which provides the patient with 10 $\mu\text{g}/\text{min}$. In the event that the shock of anaphylaxis is refractory to epinephrine, norepinephrine or dopamine can be added.²⁰

NEUROGENIC SHOCK

Neurogenic shock can be due to spinal cord injury or spinal anesthesia. The loss of sympathetic tone leads to increased venous capacitance, decreased venous return, decreased preload, decreased CO, and ultimately hypotension, often without a compensatory increased heart rate. Treatment of neurogenic shock includes careful IVF administration, and vasopressor support with α_1 stimulation for vasoconstriction with or without β_1 receptor stimulation for cardiac support. Norepinephrine and dopamine can be used for this purpose. Phenylephrine may be used as well; however, care should be taken to monitor for reflex bradycardia with this agent.

The current recommendation for blood pressure management after acute spinal injury from the American Association of Neurologic Surgeons is as follows: (1) hypotension should be avoided if possible, and if hypotension occurs, it should be corrected as soon as possible; (2) MAP goal of 85 to 90 mm Hg for the first 7 days following acute spinal cord injury. A MAP at this level is thought to improve spinal cord perfusion following injury. These recommendations are listed as options in the guideline as the data supporting these recommendations are limited.²¹

Cardiogenic Shock

Cardiogenic shock is the result of cardiac dysfunction and is usually associated with AMI. It is defined as hypotension not reversible with fluid therapy or hypoperfusion resulting in organ dysfunction, despite adequate left ventricular filling pressure. Cardiogenic shock is generally divided into two forms: left-sided failure, mainly due to AMI, and right-sided failure, which can have several causes. The right ventricle is thin walled, compared with the left ventricle, and can handle volume overload easier than the left side, which handles much higher pressures. Similarly, right ventricular function is volume dependent, whereas left ventricular function is pressure dependent.

The treatment for cardiogenic shock is based on the side primarily involved. In the clinical setting, it is reasonable to start with the electrocardiogram (EKG) in these patients. An EKG that demonstrates a left-sided AMI indicates a left ventricular cause for cardiogenic shock. This can be followed by a bedside EKG. Right ventricular dilatation indicates a right-sided cause. Echocardiography can also be used to exclude a diagnosis of cardiac tamponade in these patients.

Right ventricular failure can be caused by a wide array of clinical conditions including left-sided failure, pulmonary

embolism, pulmonary HTN, sepsis, and lung disease. The treatment of cardiogenic shock from right-heart failure is primarily directed at volume resuscitation to ensure adequate preload and at reversing the cause of the failure. Inotropic medication may be required as well. Right ventricular overfilling in the setting of heart failure can lead to a bulging intraventricular septum. This can diminish left ventricular function and decrease coronary perfusion, resulting in myocardial ischemia or infarction.²²

Cardiogenic shock from left-sided failure has been extensively studied, and most guidelines are directed at treating this form of cardiogenic shock. Since it is mainly due to AMI, treatment should be aimed at early revascularization and supportive care. According to the results of the SHOCK trial, which informed the American College of Cardiology/American Heart Association guidelines, emergency revascularization should be attempted immediately for patients younger than 75 years of age with cardiogenic shock from AMI.²³

The American College of Cardiology/American Heart Association guidelines for the pharmacologic treatment of cardiogenic shock complicating AMI are as follows: (1) if SBP is 70 to 100 mm Hg without signs and symptoms of shock, dobutamine is the first-line agent; (2) if SBP is 70 to 100 mm Hg and the patient has signs and symptoms of shock, dopamine is the first-line treatment.²⁴ If the response to these individual agents is inadequate, they can be used in combination or norepinephrine may be used with dobutamine. Vasopressin may also be used as a second-line agent.⁸ A recent prospective randomized controlled trial in ICU patients revealed that the combination of norepinephrine–dobutamine appeared to be a more reliable and safer strategy than epinephrine alone.²⁵ Epinephrine was associated with a transient lactic acidosis, higher heart rate and arrhythmia, and inadequate gastric mucosa perfusion.

TRANSIENT HYPOTENSION

Push-dose vasopressors have been utilized for years in anesthesia practice, but they have only recently become commonplace in critical care or emergency medicine practice. Phenylephrine and epinephrine are the two agents most commonly used in this setting. The indication for push-dose vasopressor treatment is limited to either transient hypotension, such as the drop in blood pressure associated with intubation, or as a bridging measure for more definitive treatment, such as the establishment of central venous access in the setting of an acutely decompensating patient.²⁶

Push-dose vasopressors are given peripherally and usually prepared in anticipation of a possible complication. As such, they should be carefully controlled and labeled. Epinephrine is typically prepared by combining 9 mL of saline solution with 1 mL of 1:10,000 epinephrine, which contains 100 μg of epinephrine. This produces a syringe of epinephrine with 10 mL at a 10 mcg/mL concentration. It is typically given in 0.5 to 2 mL boluses that result in a dose of 5 to 20 μg . The effect is typically seen within a couple of minutes and lasts 5 to 10 minutes.²⁷

Phenylephrine is also commonly utilized in this manner. It is typically prepared by inserting 1 mL of 10 mg/mL phenylephrine solution into a 100 mL bag of normal saline. This produces a concentration of 100 µg/mL. Phenylephrine is also typically dosed in 0.5 to 2 mL aliquots, resulting in a dose of 50 to 200 µg per bolus. Phenylephrine also works very rapidly but lasts 10 to 20 minutes.²⁷

Again, it should be emphasized that these agents are only for use as temporizing measures or for transient conditions. Push-dose use of these medications is not a substitute for vasopressor or inotrope infusions, which are the indicated treatment for these conditions.

CONCLUSION

The choice of pharmacologic treatment for shock can be very difficult. It is important to differentiate the cause of shock as quickly as possible. Initial treatment should be focused on maximizing fluid status before starting vasopressor therapy. In the undifferentiated shock patient, norepinephrine is a reasonable initial medication. As soon as the cause of shock is known, treatment should be adjusted to best address that cause. A solid understanding of the pathophysiology of the various types of shock is essential to making good decisions at the bedside.

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Management after Cardiac Surgery

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OVERVIEW

Cardiac surgery is one of the most commonly performed major operative procedures in the United States. The indications for cardiac surgery include myocardial ischemia and infarction, heart failure, valvular dysfunction, aortic pathology, and surgery for dysrhythmias. The management of patients following cardiac surgery requires a multifaceted approach and the involvement of a team of specialists. While the intensivist is often the point person for the management of the patients following open-heart surgery, it is essential that management involve the surgeon, cardiologist, and anesthesiologist, and a wide variety of other health care providers.

Successful postoperative management following cardiac surgery requires a clear understanding of the patient's preoperative conditions and the intraoperative events and management. The goal is to restore the patient's normal physiologic condition and homeostasis. As medical management and interventional cardiology procedures evolve and improve, the patients being referred for cardiac surgery are sicker and more debilitated than they were in the past. This trend is likely to continue in the years to come. Despite these increased challenges facing cardiac surgeons, patient outcomes remain very good in large part due to postoperative management and ICU care. A systems-oriented approach is often necessary to deal with the multitude of problems facing these patients, and the cardiac system is generally the primary determinant of recovery.¹

HEART

Hemodynamic Management

The goal of hemodynamic management is to maintain adequate oxygen delivery to the tissues and to minimize demands on a heart that has just undergone major surgery. Optimization of cardiac output is essential to maintain function of the brain, kidneys, gut, lungs, and other end organs necessary for optimal recovery. Postoperatively, contractility is almost always decreased, the magnitude of which is often related to the severity of chronic dysfunction, ischemia, and intraoperative events.²

Despite the wide array of patient disease and cardiac procedures, significant similarities exist in patient monitoring, evaluation, and management.² The majority of patients have continuous electrocardiographic (EKG) monitoring, pulse oximetry, blood pressure, central venous pressure (CVP) monitoring, and in most instances a pulmonary artery catheter (PAC) for monitoring mixed venous O₂ saturation (SvO₂), pulmonary artery pressures, and continuous cardiac output. The use of a PAC in patients undergoing cardiac surgery has been a topic of some debate.^{3,4} Although it was previously common practice to use PACs in almost every patient undergoing cardiac surgery, its utilization has decreased significantly in some areas of the United States in recent years.⁵ These modalities allow for measurement of oxygen consumption and mixed venous and arterial oxygen saturation, and an estimation of cardiac output. The goal is to maintain normal hemodynamic

values if possible since it has been shown that normal oxygen transport and normal SvO₂ (> 70%) in the immediate post-operative period can improve outcome,⁶ although achieving these targets can be challenging.⁷⁻⁹ Adjustments to volume status, afterload, heart rate and rhythm, and cardiac output can help to maximize end-organ oxygen delivery.

Blood Pressure

Mean arterial pressure (MAP) is the most dynamic physiologic variable in the first hours following cardiac surgery.² This can be due to a number of factors including decreased preload, vasodilatation, and cardiac contractility. Many patients' end organs are dependent on higher blood pressures; however, concerns about bleeding often lead to a struggle between maintaining a higher MAP for perfusion and keeping the pressure low to protect suture lines. Despite these concerns, the MAP should be maintained above 65 mm Hg. Volume resuscitation can be guided by CVP, and, although there is no gold standard for the type of fluid used for resuscitation, there is some evidence to suggest that use of colloid versus crystalloid can significantly improve hemodynamic status after cardiac surgery.¹⁰ It has been our practice to use 5% albumin, though there are concerns about albumin extravasation,¹¹ particularly in the lungs. As the patient is undergoing volume resuscitation, there are a number of pharmacologic agents (Table 20-1) that can be useful for increasing vascular tone and cardiac contractility. It is essential that the intensivist have a thorough understanding of the mechanism of each of these agents and their interactions with one another.

In addition to hypotension, some patients may present with significant levels of hypertension.^{2,12} This may lead to excessive bleeding and an increase in afterload that can exacerbate low cardiac output, and should be treated aggressively with vasodilators after adequate sedation and pain control is achieved.

Cardiac Contractility

Myocardial contractility following cardiac surgery can be a variable and dynamic process. Patients with low cardiac

output following cardiac surgery are at significant risk for end-organ hypoperfusion if the cardiac index (CI) is below 2.2. It is essential that the source for low CI be identified and treated rapidly. Once hypovolemia, bleeding, and tamponade have been ruled out, the focus should be on instituting pharmacologic and mechanical support for the failing heart. The most useful drugs (Table 20-1) have significant inotropic and vasodilatory activity.¹³ Epinephrine has both α and β effects and is very useful in the postoperative period. The β_2 effects are seen predominantly at lower doses, whereas the α effects predominate at higher doses. Both dobutamine and dopamine are effective β -agonists with broad dosage-dependent effects, but dobutamine has a superior effect on cardiac contractility. Milrinone, which is a cyclic phosphodiesterase inhibitor, works by increasing cAMP levels, leading to an increase in calcium flux and myocardial contractility. In addition to its inotropic effect, milrinone decreases vascular tone, particularly in the pulmonary bed, making it a helpful addition to the management of intraoperative and postoperative right- heart failure. A randomized trial by Feneck et al.¹³ compared the effects of milrinone and dobutamine on low-output syndrome following cardiac surgery. They found that patients receiving dobutamine had a higher CI, heart rate, and left ventricular (LV) stroke work index than those receiving milrinone, whereas milrinone led to a greater decrease in pulmonary capillary wedge pressure. Dobutamine, however, was associated with a higher incidence of hypertension and conversion from sinus rhythm to atrial fibrillation (AF).

Mechanical Support for Low Cardiac Output

Pharmacologic support is generally effective in helping separate from cardiopulmonary bypass (CPB) and in supporting CI in the postoperative period. There are situations, however, in which mechanical support is necessary, such as when the CI does not increase above 2.0 despite maximum inotropic support. The intra-aortic balloon pump (IABP) is a mechanical circulatory assist device developed in 1968 by Kantrowitz et al.¹⁴ The balloon is placed in the descending thoracic aorta



TABLE 20-1: Commonly Used Drugs Following Cardiac Surgery

Drug	Dose	Contractility	HR	MAP
Epinephrine	1–20 μ g/min	4+	3+	↑ (dose dependent)
Milrinone	0.15–0.5 μ g/kg/min	4+	0	↓↓↓
Dobutamine	2–20 μ g/kg/min	3–4+	1–2+	↓↓
Dopamine	1–4 μ g/kg/min	1+	1+	↓
	4–20 μ g/kg/min	2–3+	2+	↑↑↑
Norepinephrine	2–40 μ g/min	1+	1+	↑↑↑↑
Phenylephrine	20–200 μ g/min	0	0	↑↑↑
Vasopressin	0.01–0.04 U/min	0	0	↑↑↑↑
Nitroglycerin	10–200 μ g/min	0	1+	↓↓
Nitroprusside	0.1–10 μ g/kg/min	0	2+	↓↓↓

Data from St Andre AC, DelRossi A: Hemodynamic management of patients in the first 24 hours after cardiac surgery, *Crit Care Med* 2005 Sep;33(9):2082–2093.

just distal to the subclavian artery. The balloon inflates during diastole, increasing coronary perfusion, and deflates during systole, decreasing afterload. Its use has evolved from circulatory support of patients in cardiogenic shock to now being used as an aid to weaning patients from CPB and for postoperative low CI. It is now the most commonly used mechanical assist device, with over 100,000 implanted annually.

Despite adequate volume loading, maximum inotropic support, and the use of IABP, a small percentage of patients will not be able to be weaned from CPB or will develop severe cardiogenic shock in the perioperative period. Over the last 20 years, the use of ventricular assist devices (VADs) has helped aid the failing heart after cardiac surgery. Studies have shown that patients requiring two or more high-dose inotropes to wean from CPB had better outcomes with early VAD insertion.¹⁵ While the details of the use of VADs are beyond the scope of this chapter, it is important to understand their utility in the management of the post-cardiac surgery patient.

Rate and Rhythm

Following cardiac surgery, patients are prone to develop some form of dysrhythmia. Heart rate and conduction abnormalities are common following valvular and coronary surgery. Most surgeons place epicardial pacing leads on the atrium, ventricle, or both that are brought out in the subxiphoid region and can be helpful in assisting in management of bradycardia and atrial dysrhythmias. Augmentation of the heart rate, even when normal, to rates of 90 to 100 can be useful to increase CI. Conversely, patients may be persistently tachycardic following surgery, which may be due to stress-related catecholamine release or from a variety of drugs used in the postoperative period. This often requires no intervention.

Ventricular arrhythmias such as premature ventricular contractions and non-sustained ventricular tachycardia (VT) are not uncommon following cardiac surgery and should prompt an examination and correction of any electrolyte disturbance. Frequent episodes or periods of sustained arrhythmia may require more aggressive therapy with anti-arrhythmic drugs such as amiodarone or lidocaine and electrical cardioversion if the patient is hemodynamically compromised. These episodes should also prompt a thorough investigation of possible ischemia, particularly in coronary artery bypass graft (CABG) patients.

Atrial Fibrillation

AF may occur in up to 30% to 40% of patients undergoing cardiac surgery, with the highest incidence being in older patients and those undergoing valve and combined CABG/valve procedures.¹⁶ The cause of postoperative AF is not well understood but is likely due to reentry of multiple waves of excitation throughout the atria.¹⁷ Several factors have been associated with increased risk for postoperative AF, including advanced age, concomitant valve surgery, history of AF, CHF, COPD, and decreased LV function.¹⁸ A number of strategies have been implemented to reduce the incidence of AF.¹⁹

β -Adrenergic blockers have been extensively studied and have shown significant efficacy in reducing AF in the postoperative setting,¹⁸ as well as reducing total hospital costs.²⁰

β -Blockers should be started as early as possible in the postoperative period to reduce the incidence of AF.²¹ For patients who cannot be started on β -blockers, antiarrhythmic agents such as amiodarone and sotalol are both safe and efficacious in decreasing postoperative AF risk.²²

Despite the use of preventive measures, AF remains a significant problem in the postoperative period. Evidence suggests that proper prevention and treatment of AF may affect hospital length of stay and stroke risk.^{19,22} In most patients, AF is self-limiting and the treatment options vary based on the patient's clinical condition. One management strategy generally utilized in postoperative AF is demonstrated in Figure 20-1. For patients who are hemodynamically unstable, difficult to manage, or have a contraindication to anticoagulation, rhythm control is the preferred approach, including the use of electrical synchronous defibrillation. However, in patients who are tolerating their AF, rate control and anticoagulation is the preferred approach since many of these patients will return to sinus rhythm within 3 months.²²

BLEEDING

Both intraoperative and postoperative bleeding present a significant challenge to the surgeon and intensivist in the management of the cardiac surgery patient. Excessive bleeding requires significant blood product usage, which is costly and adds significant morbidity and mortality to the patient.²³ The need for intraoperative anticoagulation combined with the effects of platelet dysfunction and generalized inflammation from the CPB circuit lead to postoperative coagulopathy. In addition, many patients now come to the operating room with some exposure to potent antiplatelet agents such as glycoprotein IIb/IIIa inhibitors, thienopyridine antiplatelet agents (clopidogrel), or direct thrombin inhibitors (dabigatran). These agents significantly disrupt platelet aggregation and the coagulation cascade and may lead to increased postoperative coagulopathy.²⁴ In general, postoperative coagulopathy is usually multifactorial, with causes including thrombocytopenia, fibrinolysis, hypothermia, hemodilution, and residual or rebound heparin.²⁵ This generally leads to some degree of chest tube output in the range of 50 to 100 cm³/h.

The treatment of postoperative bleeding is summarized in Table 20-2 and is dependent on the judgment of the surgeon and intensivist to determine if the patient is bleeding from surgical problems or coagulopathy. Chest tube inspection and management is essential to understand the pathophysiology of the bleeding. Generally, in coagulopathic bleeding there is no clot in the chest tubes and this can often be managed with correction of the coagulopathy and administration of blood products. Some other maneuvers that can be useful include increasing positive end-expiratory pressure (PEEP), use of epsilon aminocaproic acid, and warming.^{26,27} In addition, some have advocated the use of activated recombinant

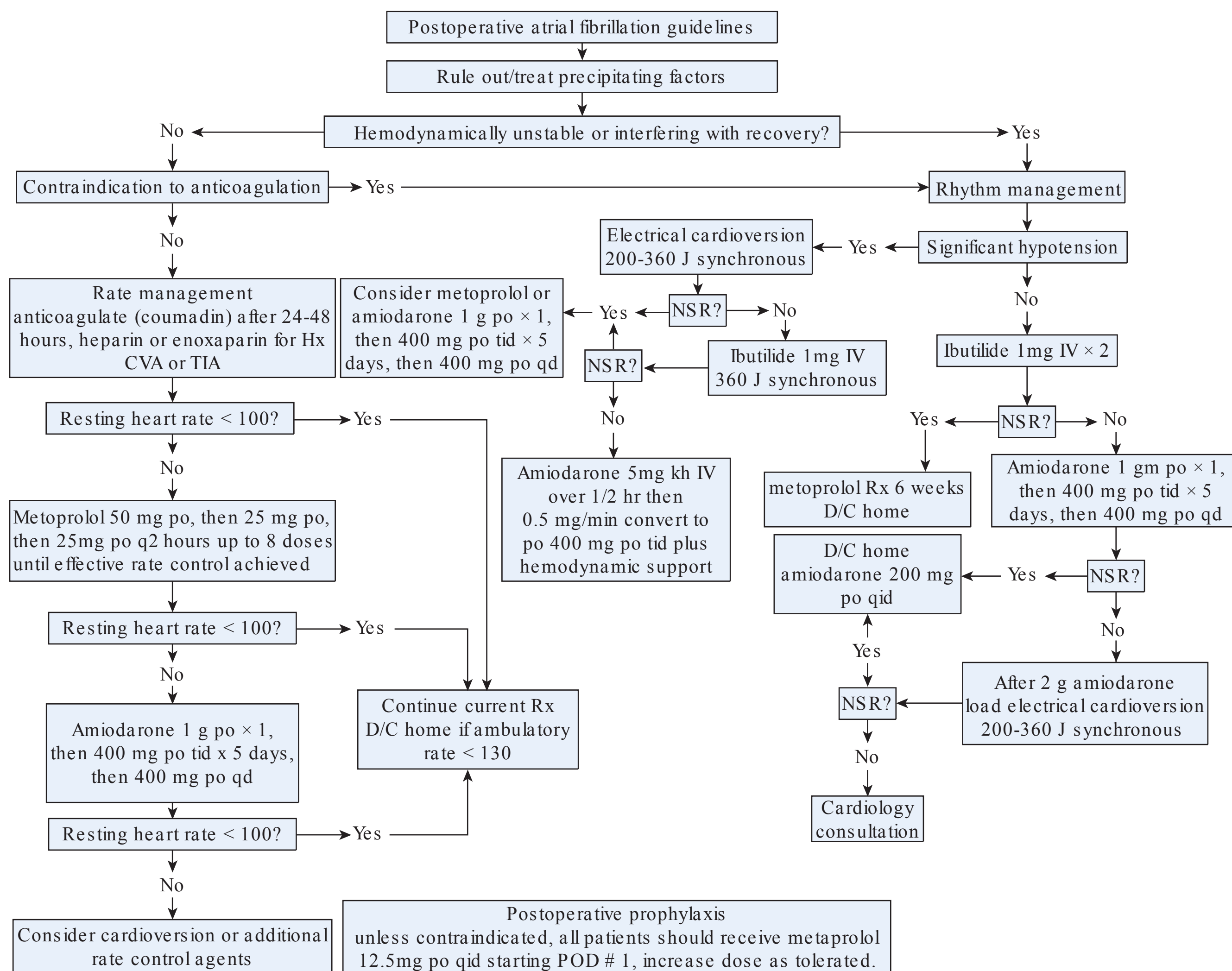


FIGURE 20-1 Management of postoperative atrial fibrillation. (Data from Khalpey Z, Ganim R, Rawn J. Postoperative care of cardiac surgery patients. In: Cohn LH, ed. *Cardiac Surgery in the Adult* and Maisel WH, Rawn JD, Stevenson WG. Atrial fibrillation after cardiac surgery. *Ann Intern Med.* 2001;135(12):1061–73.)

factor VII (rFVIIa) that has been widely reported in the management of bleeding after cardiac surgery. However, concerns about safety, particularly in bypass patients with fresh grafts, have been raised.²⁸

Mediastinal Reexploration

Approximately 30% of patients who have undergone cardiac surgery with CPB require significant blood transfusion²⁹ and 4% require reexploration.³⁰ Mediastinal reexploration should be considered when bleeding exceeds 400 mL/h for the first hour, 300 mL/h for 2 to 3 hours, and 200 mL/h for 4 hours (Table 20-2). Chest tube output is not the only indicator of significant surgical bleeding since chest tubes can become clotted and blood can collect and clot in the pericardium. A return to the operating room for reexploration should be initiated for hemodynamic instability not responsive to inotropic

support or resuscitation or for signs of tamponade such as elevated filling pressures or equalization of pressures. Widening of the mediastinum on chest X-ray (CXR) or signs of tamponade on transesophageal echocardiogram can be helpful in patients for whom the diagnosis is questionable. On rare occasions, the patient may require reexploration at the bedside if there is massive sudden hemorrhage or cardiac arrest is imminent. In those situations, the goal is to relieve the tamponade, restore cardiac contractile function, and temporarily control bleeding while the patient is returned to the operating room.

LUNG

Postoperative pulmonary care is aimed at restoring normal pulmonary capillary permeability and interstitial lung volume, preventing or treating atelectasis, maintaining normal arterial blood gases, and preventing infection.



TABLE 20-2: Management of Postoperative Bleeding

Bleeding Scenario	Diagnosis	Treatment
< 50 mL/h		
Stable BP, coagulopathy	Post-CPB	Supportive care
> 100 mL/h		
Hypothermic	Hypothermia	Rewarming strategies
Acute hypotension (MAP < 50 mm Hg)		Fluid resuscitation (goal MAP 60–65 mm Hg)
Diffuse bloody ooze	Borderline coagulopathy	
Coagulopathy		
1. High PTT, PT	Rebound heparin effect	Coagulation screen
2. INR > 1.4	Deficient clotting factors	Heparin level; protamine
3. Low fibrinogen	Deficient clotting factors	FFP
4. Platelets < $10^5/\mu\text{L}$	Thrombocytopenia	Platelets
5. Platelets > $10^5/\mu\text{L}$	Platelet dysfunction	Platelet pool
6. Bleeding > 10 min	Fibrinolysis	DDAVP
7. Bleeding > 30 min (high D-dimers, fibrinolysis)	Fibrinolysis	Tranexamic acid, aminocaproic acid
> 200 mL/h		
> 200 mL/h for 4 h	Surgical bleeding should be assumed for any of these criteria	Consider reexploration
> 300 mL/h for 2–3 h		
> 400 mL/h for 1 h		

DDAVP: desmopressin (synthetic vasopressin); PTT: activated partial thromboplastin time; FFP: fresh frozen plasma; PT: prothrombin time; BP: blood pressure; CPB: cardiopulmonary bypass. Adapted with permission from Cohn LH: *Cardiac Surgery in the Adult*, 4th edition. New York: McGraw-Hill, Inc; 2012.

Early Versus Delayed Extubation

Early extubation may be defined as extubation of a patient within 3 to 6 hours of arrival in the ICU. The goals, as with any extubation, are to have a patient who is awake enough to protect his or her airway and adequately oxygenate and ventilate. Weaning of sedation should begin early after admission to the ICU as long as the patient is hemodynamically stable with manageable chest tube output. Early extubation of patients after cardiac surgery has been associated with shorter ICU stay, shorter overall hospital stay, and improved intrapulmonary shunting, without increasing perioperative morbidity.³¹

There are a variety of approaches to rapid weaning including the rapid shallow breathing index (RSBI) that is calculated by dividing a patient's tidal volume into the observed respiratory rate during a spontaneous breathing trial of 10 to 30 minutes. Statistically, an RSBI of < 105 is thought to be highly predictive of a successful extubation (see Chapter 6, Weaning and Extubation).

A T-tube trial is another way of performing a spontaneous breathing trial. The patient has supplemental oxygen administered while remaining intubated. There is no ventilatory support. Patients who tolerate a T-piece trial have a high chance of successful extubation, presumably because breathing through a T-piece is more difficult than normal breathing.

Other clinicians rely on the traditional method of converting the ventilation mode to a partial support (assist control or

intermittent mandatory ventilation with pressure-supported [PS] spontaneous breaths) or a total spontaneous setting when the patient is fully awake. The decision to extubate is then based on clinical observation, O₂ saturation, and blood gas results. Minimum settings before extubation typically are PS of 10, with a PEEP of 5. This amount of PS helps to overcome endotracheal tube resistance, and PEEP helps to maintain and recruit alveoli. No particular weaning technique has been shown to be superior to any other, and the literature does not implicate any technique as being more commonly associated with adverse outcome.

The postoperative CXR should also factor into the decision-making process. Pulmonary edema and pleural effusions are common in the early postoperative period, but are usually not large enough to be significant. Patients who do not meet the criteria for early extubation may develop larger effusions over time that may need to be drained in order to maximize the likelihood of a successful extubation. Cardiac surgery patients are also at risk for worsening pulmonary edema; therefore, diuresis may be helpful in patients who cannot be extubated early.

Recent evidence has suggested that early extubation is not associated with increased morbidity or mortality in patients undergoing cardiac surgery, including those traditionally considered high risk.^{32,33} Rates as high as 92% have been reported for extubation within 6 hours of arrival in the cardiac ICU after isolated on-pump CABG.³⁴ Data regarding immediate extubation in the operating room have also begun

to emerge, potentially improving hospital costs and length of stay even further for certain groups of patients.^{35,36} However, this is controversial and there are concerns for inadequate pain control and the need for frequent and imperfect titration of narcotics.³⁷

Factors that may adversely impact successful early extubation include the effects of anesthesia on postoperative hemodynamics, stress responses and awareness, altered management in the control of pain, shivering and ischemia in the early postoperative period, and the risks of reintubation in patients who might require reoperation for bleeding. Risk factors for delayed extubation of postoperative CABG patients include increased age, female gender, postoperative use of IABP, inotrope requirement, bleeding, and atrial arrhythmia.³⁸

Pulmonary Management Following Extubation

Once extubated, patients will need supplementary oxygen. This is usually given as a 40% face mask, and then gradually weaned to a nasal cannula. The use of bedside incentive spirometry and chest physiotherapy will help reduce atelectasis and the risk of pneumonia. In addition, short-term β -agonists help in the postextubation recovery phase, even in patients without a history of COPD or reactive airway disease.

A median sternotomy or thoracotomy incision is associated with significant pain, splinting, and decreased chest wall compliance, resulting in shallow breaths, atelectasis, and an increased risk of pneumonia.³⁹ Adequate pain control reduces the likelihood of postoperative splinting, atelectasis, and pneumonia. Opiates combined with rapid-acting nonsteroidal anti-inflammatory drugs (NSAIDs) such as ketorolac have been used with success,⁴⁰ and the increasing availability of intravenous acetaminophen has broadened the options for non-narcotic analgesia. Patient-controlled analgesia (PCA) may have the advantage of improved pain control as well as a reduction in the occurrence of atelectasis when compared with nurse-controlled analgesia.

Pulmonary Complications

Atelectasis and pleural effusion are among the more common complications following cardiac surgery.⁴¹ In addition, there are a number of other complications (see Table 20-3) that may complicate postoperative recovery, leading to longer stays in the ICU and hospital and increasing overall morbidity and mortality. Recognizing these potential complications and treating them early is essential to ensuring a successful postoperative outcome.

Postoperative Pulmonary Dysfunction

Postoperative pulmonary dysfunction (POPD) is a constellation of events that occur in patients undergoing cardiac surgery. It may delay extubation, factor into extubation failure, and delay functional recovery. POPD involves alterations in pulmonary function such as increased work of breathing,



TABLE 20-3: Pulmonary Complications After Cardiac Surgery

Complication	Frequency (%)
Pleural effusion	27–95
Atelectasis	17–88
Prolonged mechanical ventilation	6–58
Diaphragm dysfunction	2–54
Pneumonia	4–20
Pulmonary embolism	0.04–3.2
ARDS	0.4–2
Aspiration	2
Pneumothorax	1.5

ARDS, adult respiratory distress syndrome

Data from Wynne R, Botti M. Postoperative pulmonary dysfunction in adults after cardiac surgery with cardiopulmonary bypass: clinical significance and implications for practice, *Am J Crit Care* 2004 Sep;13(5):384–393.

shallow respiration, ineffective cough, and relative hypoxemia. All postoperative cardiac surgery patients develop some degree of POPD and/or hypercapnea.

The underlying basis for POPD is the development of abnormal gas exchange and alterations in lung mechanics. Gas exchange abnormalities include a widened alveolar–arterial oxygen gradient, increased microvascular permeability in the lung, increased pulmonary vascular resistance, increased pulmonary shunt fraction, and intrapulmonary aggregation of leukocytes and platelets.⁴² Alterations in the mechanical properties of the lung lead to reductions in vital capacity, functional residual capacity, and static and dynamic lung compliance.

Premorbid conditions such as chronic obstructive pulmonary disease (COPD) and undiagnosed preoperative pneumonia can contribute to the development of pulmonary dysfunction after cardiac surgery. Postoperatively, these patients may develop pulmonary edema, atelectasis, or pneumonia. The risk of developing pneumonia increases with delayed extubation after CABG or valve surgery.⁴³ In addition, shallow breathing, a weak cough, and splinting from inadequate pain control can also contribute to the development of PPD, leading to respiratory failure and reintubation.

CPB can contribute to pulmonary dysfunction by increasing left atrial or pulmonary venous pressure. These effects combined with reduced plasma oncotic pressure can increase extravascular lung water.^{44,45} During CPB, cytotoxic and vasoactive mediators of the inflammatory response^{46–50} and circulating microemboli⁵¹ may reach the lung via bronchial arteries. This inflammatory response has been termed “pump lung” or “postpump syndrome.” These agents increase pulmonary capillary permeability, perivascular edema, and bronchial secretions. Once CPB commences, the cessation of pulmonary ventilation results in collapsed lungs and insufficient alveolar distention to activate the production of surfactant, a situation that potentiates alveolar collapse. Abnormal pulmonary mechanics, retention of secretions, and atelectasis can also occur.⁴²

The cumulative effect of premorbid conditions and CPB contributes to the development of an increased work of

breathing, postoperative atelectasis, pulmonary edema, as well as an increased susceptibility to infection.

Pleural Effusions

Pleural effusions are common after cardiac surgery, including CABG, and can be categorized as: perioperative (within the first week), early (within 1 month), late (2–12 months), or persistent (after 6 months).⁵² Among patients undergoing CABG, the prevalence of pleural effusions in the immediate postoperative period is high. In the week after CABG, the reported prevalence of pleural effusions has ranged from 40% to 75%.^{53–57} Most effusions are small, unilateral, left-sided, and asymptomatic. In a study by Labidi et al., almost 7% of patients had a clinically significant pleural effusion in the 30 days postsurgery.⁵⁸ Peng et al. conducted a similar study of 356 patients who were available for evaluation 1 month after undergoing CABG. The initial diagnosis of a newly developed symptomatic large pleural effusion was made in 11 patients (3.1%) within 30 days of CABG. Eight had a pleural effusion predominantly on the left side and three on the right.⁵⁹ When the presence of a pleural effusion hinders extubation or causes pulmonary dysfunction, tube thoracostomy, thoracentesis, or placement of a pigtail catheter may be indicated.

Pulmonary Edema

CPB can cause cardiogenic pulmonary edema from hemodilution, volume overload, and reduction in oncotic pressure. It can also cause noncardiogenic pulmonary edema (NCPE) by producing a systemic inflammatory response syndrome (SIRS). This involves an increase in capillary permeability and accumulation of extravascular lung water. Surfactant production is also decreased, resulting in atelectasis. Other potential causes of postoperative NCPE include blood transfusions, the administration of fresh frozen plasma to control bleeding, and preexisting lung conditions.⁶⁰ Additionally, protamine sulfate, which is often given to reverse the effects of heparin intraoperatively, has been associated with causing NCPE on rare occasions.⁶¹

Most cases of postoperative pulmonary edema are mild and can be treated with early diuresis. Fulminant NCPE, although rare, is associated with a high mortality. SIRS can progress to full-blown adult respiratory distress syndrome (ARDS). This syndrome is diagnosed by the presence of bilateral patchy infiltrates on CXR, normal cardiac filling pressures, relative hypoxemia, and a $\text{PaO}_2/\text{FiO}_2$ ratio of < 200 . Management of NCPE or ARDS involves mechanical ventilation with as low an FiO_2 as possible to maintain a PO_2 of 60 to 70. Higher settings of PEEP may be needed and must be balanced with the effect of reducing cardiac output by reducing venous return. Ventilator settings with a tidal volume of 6 mL/kg of predicted body weight have been shown to improve survival when compared with higher tidal volume.

Other maneuvers that may be useful in the management of ARDS include prone positioning, which improves oxygenation but poses safety concerns in the poststernotomy patient,

and high levels of PEEP (35–40 cm H_2O), which have not been shown to improve survival. High-frequency oscillatory ventilation is, in theory, the ideal “lung-protective” method, but its benefits have not been proven. Diuresis in the early postoperative period may assist with careful managing of fluid status in patients with impaired pump function; however, no particular drug therapy, including corticosteroids, has been shown to improve survival in patients with ARDS. Inhaled nitric oxide, although useful in decreasing pulmonary vascular resistance and decreasing right heart failure, has no substantial impact on the duration of ventilatory support or mortality.

RENAL

Patients undergoing cardiac surgery often have some degree of peripheral vascular disease, diabetes, or other predisposing factors that impact renal function. Patients at risk for developing postoperative acute kidney injury (AKI) include those of increasing age, as well as those with a history of hypertension, diabetes mellitus, and CHF. It has been generally accepted that patients requiring lengthy procedures on bypass are at increased risk^{62–64}; however, the causality and degree of this relationship is controversial^{65–67} and any effects on kidney function may not be long-term.⁶⁸ Regardless, AKI is a major complication of CABG surgery that is strongly associated with in-hospital morbidity and mortality, even with mild elevations in creatinine.⁶⁹ Up to 30% of patients who undergo CABG develop some degree of acute renal impairment⁷⁰ and postperfusion proteinuria occurs in many patients.⁷¹ The incidence of AKI may be increasing despite a trend of decreasing in-hospital mortality. Some have suggested that this is due to broader criteria for the diagnosis.⁷²

The Society of Thoracic Surgeons National Cardiac Surgery database defines postoperative new renal failure as a serum creatinine of > 2.0 mg/dL, doubling of peak preoperative creatinine, or requirement of dialysis. The Acute Dialysis Quality Initiative formulated the Risk, Injury, Failure, Loss, and End-Stage Kidney (RIFLE) classification.⁷³ RIFLE defines three grades of increasing severity of AKI—risk (class R), injury (class I), and failure (class F)—and two outcome classes (loss and end-stage kidney disease). The RIFLE classification grading is based on changes in either serum creatinine or urine output from the baseline condition (see Table 20-4).⁷⁴

Renal Protection

AKI can be classified on the basis of the underlying pathology. The majority of postoperative AKI is due to acute tubular necrosis (ATN) or prerenal azotemia. Postobstructive uropathy and glomerulonephritis can also occur. Prerenal azotemia often develops from hypoperfusion and ischemia, but is effectively managed by restoration of normal blood flow. This may be accomplished with volume supplementation with fluid or blood, or increasing cardiac output with inotropes. ATN is thought to arise from a variety of insults to the kidney in



TABLE 20-4: Risk, Injury, Failure, Loss, and End-stage Kidney (RIFLE) Classification

Class	Glomerular Filtration Rate Criteria	Urine Output Criteria
Risk	Serum creatinine $\times 1.5$	$< 0.5 \text{ mL/kg/h} \times 6 \text{ h}$
Injury	Serum creatinine $\times 2$	$< 0.5 \text{ mL/kg/h} \times 12 \text{ h}$
Failure	Serum creatinine $\times 3$, or serum creatinine $\geq 4 \text{ mg/dL}$ with an acute rise $> 0.5 \text{ mg/dL}$	$< 0.3 \text{ mL/kg/h} \times 24 \text{ h}$, or anuria $\times 12 \text{ h}$
Loss	Persistent renal failure. Complete loss of kidney function > 4 weeks	
End-stage kidney disease	Complete loss of kidney function > 3 months	

For conversion of creatinine expressed in conventional units to SI units, multiply by 88.4. RIFLE class is determined based on the worst of either glomerular filtration criteria or urine output criteria. Glomerular filtration criteria are calculated as an increase of serum creatinine above the baseline serum creatinine level. Acute kidney injury should be both abrupt (within 1–7 days) and sustained (more than 24 hours). When the baseline serum creatinine is not known and patients are without a history of chronic kidney insufficiency, it is recommend to calculate a baseline serum creatinine using the Modification of Diet in Renal Disease equation for assessment of kidney function, assuming a glomerular filtration rate of $75 \text{ mL/min/1.73 m}^2$. When the baseline serum creatinine is elevated, an abrupt rise of at least 0.5 mg/dL to more than 4 mg/dL is all that is required to achieve class failure. Reproduced with permission from Hoste EAJ, Clermont G, Kersten A, et al: RIFLE criteria for acute kidney injury are associated with hospital mortality in critically ill patients: a cohort analysis, *Crit Care* 2006;10(3):R73.

these patients, including ischemia, general anesthesia, radio-contrast dyes, and heart failure.

Blood flow decreases in the early phase of ATN, and therefore vasodilators theoretically should reduce necrosis in the kidney by restoring blood flow to the tubules. Fenoldopam, a dopamine analog, increases renal blood flow and decreases renal vascular resistance in a dose-dependent fashion when infused at 0.1 to 0.3 mcg/kg/min .⁷⁵ A 2008 meta-analysis of 13 studies determined that patients receiving fenoldopam had decreased need for renal replacement therapy, in-hospital mortality, time on mechanical ventilation, and time in the ICU. However, its use was also associated with perioperative hypotension and the need for vasopressors.⁷⁶

CPB and cardioplegic arrest are associated with free-radical formation. These free radicals are thought to cause damage to various organs, including the kidneys. Several studies have looked at free-radical scavenging with agents such as *N*-acetylcysteine as a way to preserve renal function; however, recent meta-analyses have concluded that the data do not support its routine use for renal protection after cardiac surgery.^{77,78}

Prognosis

Ryckwaert et al., in a study of 591 patients, determined that a postoperative 20% increase in plasma creatinine after cardiac surgery was associated with an increase in mortality, especially when accompanied by multiple organ dysfunction.⁷⁹ When acute renal failure is severe enough to require renal replacement therapy (RRT), mortality rates are 50% to 90% compared with $< 3\%$ for patients without AKI.^{70,80} Possible explanations for the increased mortality associated with AKI are salt and water retention resulting in volume overload, hyperkalemia, and acid–base derangements.⁸¹ These derangements may result in hypertension, hypotension, changes in cardiac output, as well as changes in blood flow to the liver and other organs.

There is evidence that AKI may lead to insulin resistance and protein breakdown, and immunocompromise.⁸²

Patients with AKI also have a high incidence of infectious complications⁸³ and frequently develop anemia and thrombocytopenia. Finally, AKI itself can lead to a non-infectious, pro-inflammatory response with activation of leukocytes, secretion of pro-inflammatory cytokines, and recruitment of neutrophils and macrophages with resultant lung injury, as has been demonstrated in animal models of ischemia–reperfusion-induced acute renal failure.^{84,85}

GASTROINTESTINAL TRACT

Gastrointestinal (GI) maladies are infrequent but serious complications of cardiac surgery, with high rates of morbidity and mortality. The incidence is low, ranging from 0.41% to 2.0% .^{86–90} However, the mortality rate has been reported to be as high as 63% ,^{88–91} with minimal improvement over the last decade. Patients most at risk for dying^{88–91} include those with New York Heart Association (NYHA) class IV and unstable symptoms, an increased need for preoperative IABP support, the need for GI surgical intervention, and patients with ischemic bowel. Zacharias et al. identified eight parameters that predicted GI complications: age greater than 70 years, long duration of CPB, need for blood transfusions, reoperation, triple vessel disease, NYHA functional class IV, peripheral vascular disease, and CHF. They suggest that intra-abdominal injury is usually ischemic in nature due to low cardiac output, hypotension, blood loss, or intra-abdominal atheroemboli.⁹² Other patients at risk include those with combined CABG–valve operations, prolonged ventilation time, female sex, need for vasopressors, sternal wound infection, and a history of peptic ulcer disease.^{88,90,93}

The list of potential complications includes GI bleeding (most common), acute pancreatitis, perforated peptic ulcer, intestinal ischemia, cholecystitis, and small bowel obstruction.^{90,94,95} Interestingly, Mangi et al., in their study of 8,709 patients, found the most frequent serious GI complication to be mesenteric ischemia, which developed in 67% of patients who suffered a serious GI complication.⁸⁷

Postoperative Care

Postoperatively, it is important to maintain GI perfusion and an adequate CVP. The common etiologic factor in developing GI complications of any kind after cardiac surgery seems to be postoperative splanchnic hypoperfusion⁹⁶ resulting in mucosal ischemia.⁹³ CPB has been shown to decrease gastric pH, increasing the risk of erosion and bleeding. Stress ulcer prophylaxis with proton pump inhibitors may reduce this risk.^{97,98} Other postoperative preventive measures that have had variable results in the literature include selective gut decontamination, early enteral feeding, and adjuvants to promote gut function such as glutamine, fiber, and growth hormone.⁹⁹

Ideally, patients are extubated early in the postoperative period and are started on oral diets. For patients who are unstable or in whom complications develop that necessitate a prolonged intubation, early enteral feeding should be considered. Enteral nutritional support for critically ill patients is thought to maintain GI mucosal integrity and barrier function, and stimulate splanchnic and GI-associated lymphoid tissue blood flow. Further, when compared with parenteral nutrition, enteral nutrition improves substrate utilization, reduces the risk of sepsis, and decreases cost.¹⁰⁰ Patients who require longer perioperative antibiotic coverage are at risk of developing *Clostridium difficile* colitis, which can significantly increase postoperative morbidity and mortality, particularly in the already immunocompromised patient. Cautious antibiotic use associated with probiotic prophylaxis could decrease the incidence of this significant complication.

NEUROLOGIC COMPLICATIONS

Incidence

Stroke and other neurologic impairments are among the most dreaded complications of cardiac and cardiovascular surgery for both the surgeon and the patient. The incidence of perioperative stroke varies between 1% and 5% and is associated with a multitude of risk factors.^{101,102} Strokes occurring within the first 24 hours after surgery have been described as more severe with higher mortality.¹⁰³ Cognitive deterioration after cardiac surgery is far more common, although the incidence varies widely. It may affect as many as 80% of patients a few days after surgery and may persist in up to one third of patients.¹⁰⁴

With advances in aortic surgery allowing broader and more frequent interventions on both an elective and emergent basis, the application of cerebral and spinal cord protective mechanisms has become of paramount importance. The three main types of neuroprotection during cardiac surgery are hypothermic circulatory arrest, antegrade cerebral perfusion, and retrograde cerebral perfusion. Hypothermia causes a decrease in cord metabolism, decreasing local energy requirements and prolonging the amount of time with which aortic resections can be performed. While stroke rates appear to be comparable between methods, patients undergoing hypothermic circulatory arrest with or without selective antegrade cerebral perfusion may experience improved recovery

from focal neurologic deficits compared to patients undergoing retrograde cerebral perfusion.¹⁰⁵

Other techniques used to reduce the incidence of cord injury include distal clamping of the aorta with perfusion of the pelvic and lower abdominal circulatory beds¹⁰⁶ and perioperative drainage of cerebrospinal fluid to decrease CSF pressure (CSFP), though randomized data for the latter exist primarily for patients undergoing thoracoabdominal aneurysm repair.¹⁰⁷ It should be mentioned that CSF drainage should be done with caution in order to minimize the risk of brain herniation.

Neurologic injury after cardiac surgery can be classified into two types. Type I includes stroke, seizures, stupor, or coma. Type II is more common and includes intellectual deterioration and memory deficit. The pathophysiology of these complications is not well understood and, although they are presumed to be largely caused by microemboli, this relationship has not been well established.¹⁰⁸ There may also be a contribution from the effects of general anesthesia. Some have theorized that the degree of aortic manipulation and clamping during cardiac surgery may be the predominant cause of neurologic injury later.¹⁰⁹

Patients at Risk

The incidence of stroke has a higher association with multi-valve surgery versus single-valve, combined CABG/valve or CABG surgery alone.¹⁰² In a study of cardiac patients over 10 years and with 2-year follow up, the strongest risk factors for both early and late stroke were advanced age (> 65), history of previous stroke or transient ischemic attack (TIA), peripheral vascular disease, CABG combined with valve surgery, or valve surgery alone.¹⁰¹

Hammon identified several risk factors for neurologic damage (Figure 20-2) including age, proximal aortic atherosclerosis, history of neurologic disease, diabetes mellitus, and history of hypertension.¹¹⁰

Postoperative Care and Prevention

The observation of a patient's neurologic decline after surgery is most distressing to family members. Early neurocognitive

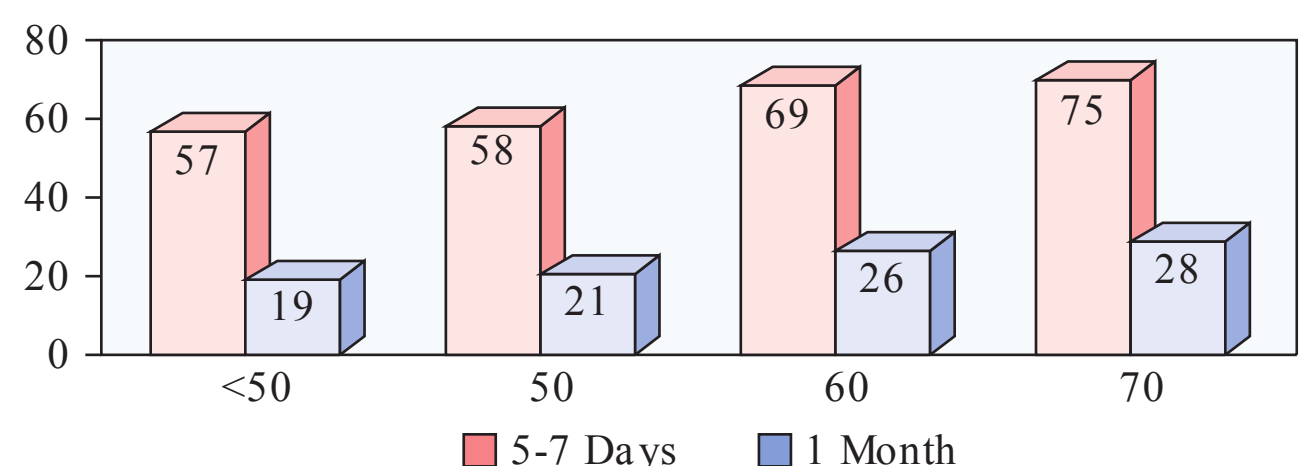


FIGURE 20-2 Effect of age by decade on neuropsychological outcome after coronary artery bypass graft surgery. Abnormal neuropsychological outcomes at 1 week and 1 month postoperatively are more common with advancing age. Percentages of patients with deficits on two or more tests are shown ($n = 374$). (Reproduced with permission from Cohn LH: *Cardiac Surgery in the Adult*, 3rd edition. New York: McGraw-Hill; 2008.)

dysfunction (within 3 months of operation) is most likely related to a combination of factors that include micro-emboli, relative hypotension, general anesthesia, and the overall inflammatory condition initiated by CPB. Neurocognitive deficits that are present after 3 months are often permanent.¹¹⁰

There is evidence that late cognitive changes are more likely related to the presence of preoperative neurologic conditions. Patients with atherosclerotic disease that has progressed enough to require CABG often have a similar degree of cerebrovascular disease. Many have had silent cerebrovascular events. Perioperative carotid endarterectomy or stenting in patients with significant carotid artery disease helps to reduce the incidence of postoperative neurologic complications. Studies have demonstrated that neurocognitive outcomes in patients who underwent standard CABG did not differ from those in a comparable control group without surgery at both 1 and 3 years, suggesting that neurocognitive decline is not due to the surgical procedure or CPB.^{111–113}

On-pump versus off-pump procedures also do not seem to make a difference. The Best Bypass Surgery trial compared neurocognitive outcomes between off-pump patients and those patients who underwent on-pump CABG with CPB. They concluded that “in elderly high-risk patients, no significant difference was found in the incidence of cognitive dysfunction 3 months after either off-pump or on pump CABG.”¹¹⁴

Maintaining stable respiratory and hemodynamic status as well as appropriate body temperature intraoperatively and postoperatively (for at least 8 hours) are all important aspects of protecting the patient’s neurologic function. This is especially true for patients undergoing deep hypothermia and circulatory arrest (DHCA) or exclusion of blood supply to the spinal cord. Maintaining adequate sedation, analgesia, and paralysis decreases the metabolic requirement of the brain in the early irritable phases of recovering function. Proper oxygenation and ventilation, along with stable hemodynamics, normothermia, and controlled blood glucose levels provide a hospitable environment for the brain.

The use of nitric oxide (NO) and oxygen radical scavengers such as mannitol has also been advocated. NO is a potent short-acting vasodilator which regulates cerebral vascular tone, inhibits aggregation of platelets and neutrophils, improves cerebral perfusion, and accelerates recovery of high-energy molecules.

Repair of thoracic aortic pathologies, such as aneurysm or dissection, whether performed via an open or endovascular technique, is associated with a greater degree of spinal cord perfusion-related impairment. Maintaining a relatively high MAP (80–90 mm Hg), low CVP (< 10 mm Hg) and low CSFP (< 10 mmHg) are not only means of neuroprotection but also serve as potentially therapeutic modalities if peripheral neurologic deficit should occur. By appropriately increasing MAP (generally by inotropic support) or cautiously decreasing CSFP, there may be complete recovery of spinal cord-related neurologic deficits (SCPP = MAP - CSFP).

ENDOCRINE

Hyperglycemia in ICU patients has been shown to increase both morbidity and mortality, even in nondiabetic patients.¹¹⁵ Several trials have shown the benefits of intensive insulin therapy in critically ill patients, and particularly in patients undergoing cardiac surgery.¹¹⁶ A trial by van den Berghe et al. showed significant decreases in mortality, bloodstream infections, acute renal failure, blood transfusions, and critical care polyneuropathy in patients managed with strict glucose control.¹¹⁷ Many centers have since tried to achieve strict glycemic control with a goal of blood glucose levels between 80 and 110 mg/dL.

The benefits of intensive glucose control in critically ill patients have recently come into question. Some trials have shown no benefit to intensive glucose control¹¹⁸ as well as an increase in the incidence of hypoglycemia.^{118,119} The Normoglycemia in Intensive Care Evaluation—Survival Using Glucose Algorithm Regulation (NICE-SUGAR) trial showed that intensive glucose control in critically ill adult patients actually increased the risk for death by 10%.¹²⁰

The investigators reported that intensive glucose control increased the absolute risk of death at 90 days by 2.6 percentage points, and that the difference in mortality was significant even after adjusting for potential confounders. Hypoglycemia was “significantly more common” in the intensive control group. The authors concluded that intensive glucose control increased mortality among adults in the ICU and that a blood glucose target of 180 mg/dL or less resulted in lower mortality than did a target of 81–108 mg/dL. Intensively lowering blood glucose to a target of 81 to 108 mg/dL does not benefit critically ill patients and may well increase their risk of dying.

The cost of intensive insulin therapy may also outweigh the benefits. Intensive glucose control involves insulin infusions that require close monitoring. This may also increase expenditures as well as workload for the intensive care unit staff. At this time, a reasonable approach to hyperglycemia should have the goals of maintaining blood glucose levels as close to normal as possible with minimal fluctuations, hypoglycemia, or hypokalemia.

Relative adrenal insufficiency (RAI) has been reported to range from 25–77% of patients undergoing cardiac surgery with cardiopulmonary bypass.^{121,122} RAI leads to inadequate concentrations of plasma cortisol and an increased and prolonged dependency on vasopressors in the postoperative period to maintain homeostasis. Factors contributing to RAI include exogenous glucocorticoids, severe illness or physiologic stress, and the use of the anesthetic etomidate, which inhibits the conversion of deoxycortisol to cortisol.^{121,123} Symptoms of adrenal crisis include hypotension, fever, and hypoglycemia, among others, and may be difficult to distinguish from complications of surgery, especially in the critically ill cardiac patient. Administration of hydrocortisone should be performed early if an adrenal crisis is suspected.

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Treatment of Mechanical Circulatory Support Devices in the Emergency Department

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INTRODUCTION

Mechanical circulatory support devices (MCSDs) are flow pumps designed to augment function of the failing ventricle. These devices can be used to support either or both ventricles, and may be for temporary or long-term use. Based on their underlying mechanics, they may be classified as counterpulsation pumps, pneumatic pumps, centrifugal pumps, or axial-flow pumps¹ (Tables 21-1 and 21-2). Though most MCSDs will neither be placed nor present to an emergency department (ED), knowledge of them can be helpful. In this chapter, we begin with a brief description of the various MCSDs, then focus specifically on the complications and emergencies associated with the device seen most in the ED: the left ventricular assist device (LVAD).

TYPES OF MECHANICAL CIRCULATORY DEVICES

1. Intra-Aortic Balloon Pump

The Intra-Aortic Balloon Pump (IABP) is a counterpulsation device commonly used for temporary circulatory support. The term “counterpulsation” refers to the inflation of the balloon in diastole and deflation in systole.

Mechanics: The IABP device consists of two major components: a double-lumen 8.0–9.5 French catheter, with a 25- to 50-ml polyethylene balloon attached at its distal end; and a console with a pump to drive the balloon. The appropriate balloon size is selected on the basis of the patient’s height. The IABP catheter is inserted percutaneously, most commonly into the femoral artery. Under fluoroscopic guidance, it is advanced into the descending thoracic aorta, with its tip 2 to

3 cm distal to the origin of the left subclavian artery (at the level of the carina). The outer lumen of the catheter is used to inflate the balloon with helium gas up to 80% to 90% of the diameter of the descending aorta. The inner lumen is used for monitoring systemic arterial pressure. The inflation of the balloon leads to volume displacement of the blood proximally and distally. This augments the coronary blood flow by augmenting the natural “Windkessel Effect” of the aorta, and potentially also improves systemic perfusion. The rapid deflation during systole leads to a decrease in afterload, thus facilitating unloading of the ventricle. The balloon is triggered using either the EKG or the systemic arterial waveform. Depending on the patient’s hemodynamic status, the balloon can be programmed to assist every beat (1:1) or less often (1:2, 1:4, or 1:8). The device should never be left unused in situ, as this may lead to thrombosis.²

Physiologic Effects: Due to the counterpulsation mechanism, the IABP causes a decrease in systolic pressure and an increase in diastolic pressure in the aorta. This translates into a decrease in the left ventricular systolic and end-diastolic pressure. The underlying principle is to increase coronary blood flow, therefore myocardial oxygen supply. By decreasing the afterload, it also leads to a decrease in the myocardial oxygen demand.²

Indications: The IABP is most commonly used as a temporizing measure in the setting of acute myocardial infarction with cardiogenic shock. It can also be used in refractory angina while the patient is awaiting revascularization. Other indications include post-cardiac surgery if the patient is unstable after weaning from cardiopulmonary bypass, refractory ventricular arrhythmias, and in some cases of acute mitral regurgitation, in which reduction in afterload may help maintain hemodynamic stability.²



TABLE 21-1: Classification of Mechanical Circulatory Support Devices Based on Duration of Therapy

Temporary Devices	Long-term Devices
Intra-aortic balloon pump	Total artificial heart (Syncardia Systems, Inc)
Extra-corporeal membrane oxygenation	HeartMate II
Centrimag®(Thoratec)	Jarvik 2000
TandemHeart System® (CardiacAssist, Inc.)	HeartWare; HVAD
Impella®system (Abiomed)	

2. Extracorporeal Membrane Oxygenation (ECMO)

For details, see the Extracorporeal Membrane Oxygenation, Chapter 9.

3. Centrimag® (Thoratec Corporation, Pleasanton, CA)

The CentriMag® is an extracorporeal, surgically implanted centrifugal pump. It is a temporary device currently approved by the Food and Drug Administration (FDA) for LV support up to six hours and RV support for up to 30 days (as a Humanitarian Use Device). The device may also be used for biventricular support.³

Mechanics: The cannulae are inserted through a midline sternotomy, with or without cardiopulmonary bypass. For right ventricular support, the inflow cannula is inserted into the right atrium and the outflow cannula to the main pulmonary artery. When used for left ventricular support in patients in whom myocardial recovery is a possibility, the inflow is obtained through left apical cannulation, or by inserting a cannula in the left atrium and through the mitral valve to the left ventricle. If myocardial recovery is not expected, the left atrium is cannulated directly. The outflow cannula is positioned within the ascending aorta.⁴ The pump is outside the body and consists of a magnetically suspended impeller that draws blood through a rotational motion and directs it toward the outflow tract. There are no mechanical bearings or seals, therefore minimizing friction between the blood and pump surfaces.

Physiologic Effects: The pump can generate up to 10 L/min of blood flow, and the speed can be adjusted to maintain a normal cardiac index.⁵ There is a risk of thrombosis; thus, patients must be maintained on anticoagulation. The device does cause hemolysis, and bleeding complications may occur.

Indications: The right ventricular device is used for acute right heart failure, most commonly in the setting of long-term LVAD use. Other indications for single or biventricular Centrimag support include acute cardiogenic shock, end-stage heart failure awaiting or ineligible for transplant, patients with postcardiotomy circulatory shock, or primary graft failure in post-transplant patients.⁶

4. TandemHeart System® (CardiacAssist, Inc., Pittsburgh, PA)

The TandemHeart is a percutaneous, continuous-flow, centrifugal blood pump that can be used to support either or both ventricles. It is Food and Drug Administration (FDA) approved for use up to 6 hours, although longer use (up to two weeks) has been reported.

Mechanics: The TandemHeart is similar to the Centrimag device in its use of an electromagnetically suspended impeller. The oxygenated blood is drawn from the left atrium using a 21F cannula inserted via the transseptal approach. The blood is pumped back to systemic circulation using a 17F femoral artery catheter, effectively bypassing the left ventricle. The right ventricle is bypassed by placing the inflow catheter in the RA and the outflow cannula in the PA.³

Physiologic Effects: The TandemHeart significantly reduces preload and augments cardiac output by pumping up to 4 L/min of blood. It decreases myocardial oxygen demand by unloading the ventricle. It is also associated with bleeding, thrombosis, and leg ischemia.

Indications: The device can be placed in the cardiac catheterization lab and was originally used to support patients during high-risk percutaneous interventions. It has since been used successfully for postcardiotomy heart failure and cardiogenic shock.

5. Impella® System (Abiomed, Danvers, MA)

The Impella is a percutaneous, axial-flow pump that is used to unload the left ventricle for short-term support, typically



TABLE 21-2: Classification of Mechanical Circulatory Support Devices Based on Mechanism of Action

Counterpulsation (Pulsatile Flow)	Pneumatic Pump (Pulsatile Flow)	Centrifugal (Continuous Flow)	Axial Flow (Continuous Flow)
Intra-aortic balloon pump	Total artificial heart	Extra-corporeal membrane oxygenation	Impella®system
	Paracorporeal ventricular assist device (PVAD)	Centrimag®(Thoratec)	HeartMate II
	HeartMate XVE	TandemHeart System®	Jarvik 2000
		HVAD	
		HeartWare	

up to five days. There are newer experimental iterations to support the right ventricle.

Mechanics: The device is mounted on a pigtail-tipped catheter that is inserted in a retrograde fashion across the aortic valve through a femoral artery sheath. The pump sits in the left ventricle and pumps blood out to the ascending aorta. The newer version, the Impella®5.0, is larger and requires surgical cut-down of the femoral or axillary artery.

Physiologic Effects: The device can augment cardiac output by about 2.5 to 5.0 L/min depending on the version used. It also leads to a decrease in myocardial oxygen demand by decreasing the afterload.

Indications: It is used most successfully in patients with acute left ventricular failure. Contraindications include LV thrombus, moderate aortic stenosis or aortic insufficiency, recent stroke or transient ischemic attack (TIA), and structural abnormalities of the ascending aorta.

6. Total Artificial Heart (SynCardia Systems, Inc., Tucson, AZ)

The Total Artificial Heart (TAH) is a pneumatically driven, pulsatile pump that is approved for temporary use but may be used as destination therapy under the Humanitarian Use Device designation.

Mechanics: The TAH is a completely artificial heart with tilting disk valves and short outflow grafts replacing the ventricles, the proximal aorta, the pulmonary artery, and the four valves. The artificial left ventricle is connected to the patient's left atrium via a left atrial inflow connector and to the patient's aorta via an outflow cannula. The artificial right ventricle is similarly connected to the patient's right atrium and pulmonary artery. The size requirements for this device include a body surface area $\geq 1.7 \text{ m}^2$ and chest AP diameter $\geq 10 \text{ cm}$ for the 70 cc device.³

Physiologic Effects: The device takes over the entire function of both ventricles. The known complications are infections, bleeding, and strokes.⁷

Indications: The device is used as a bridge to transplantation in patients with biventricular failure. The recently approved wearable controller allows discharge home; therefore, it is now also being used in patients with end-stage heart failure who are not transplant candidates.

Left Ventricular Assist Devices (LVADs)

Left Ventricular Assist Devices (LVADs) are blood pumps designed to augment the pressure and flow functions of the failing left ventricle. They draw blood out of the left heart either from the ventricle or atrium. Implantable pumps today aspirate blood from the apex of the left ventricle and reinfuse it into the ascending aortic arch. LVAD are either volume displacement pulsatile pumps or continuous flow rotary pumps. Over the past 15 years, clinical application has gradually shifted from primarily pulsatile machines to continuous-flow machines. Pumps can be used for right ventricular assistance (RVAD), biventricular assistance (BiVAD), or total circulatory

support (total artificial heart). Each of these has its respective indications, but none is as commonly implanted as the LVAD.

Types of Devices

In 2015, the two primary devices being manufactured in the United States are Thoratec's HeartMate II⁸ and the Heartware HVAD.⁹ Several LVADs (HeartMate III) are in clinical-trial phase along with a few older devices (Heartmate XVE and Jarvik 2000). Each of these has important distinctions that cannot be fully discussed in this chapter. Both the HeartMate II and HVAD are continuous-flow pumps. The initial volume displacement pumps were pulsatile in the hope of mimicking normal human physiology as much as possible. These initial devices had favorable flow attributes, but they were large and had poor durability resulting from their multiple moving parts. The liabilities of the higher shear stress and attenuated pulsatility characteristic of continuous-flow LVADs are offset by their smaller size and reliability.¹⁰ Increased gastrointestinal bleeding, pump thrombosis, thromboembolism, and lower rates of left ventricular recovery are cited disadvantages of continuous-flow pumps.^{11,12}

The major mechanical difference between HeartMate II and Heartware is the vector of flow within the device. The HeartMate II uses a single impellar supported by blood-washed thrust bearings, creating axial flow through the device (Figure 21-1). The impellar draws blood in through the inlet cannula and linearly propels blood out the outlet cannula. The Heartware device uses a vortex model in which blood is centrifugally propelled outward via a circular cartridge. The advantages of the centrifugal approach are smaller device size and potentially less sheer stresses applied to the blood products.¹³

Future products include transcutaneously powered devices that may substantially reduce the risk of driveline infections and allow patients exposure to water not allowed with current devices.¹⁴

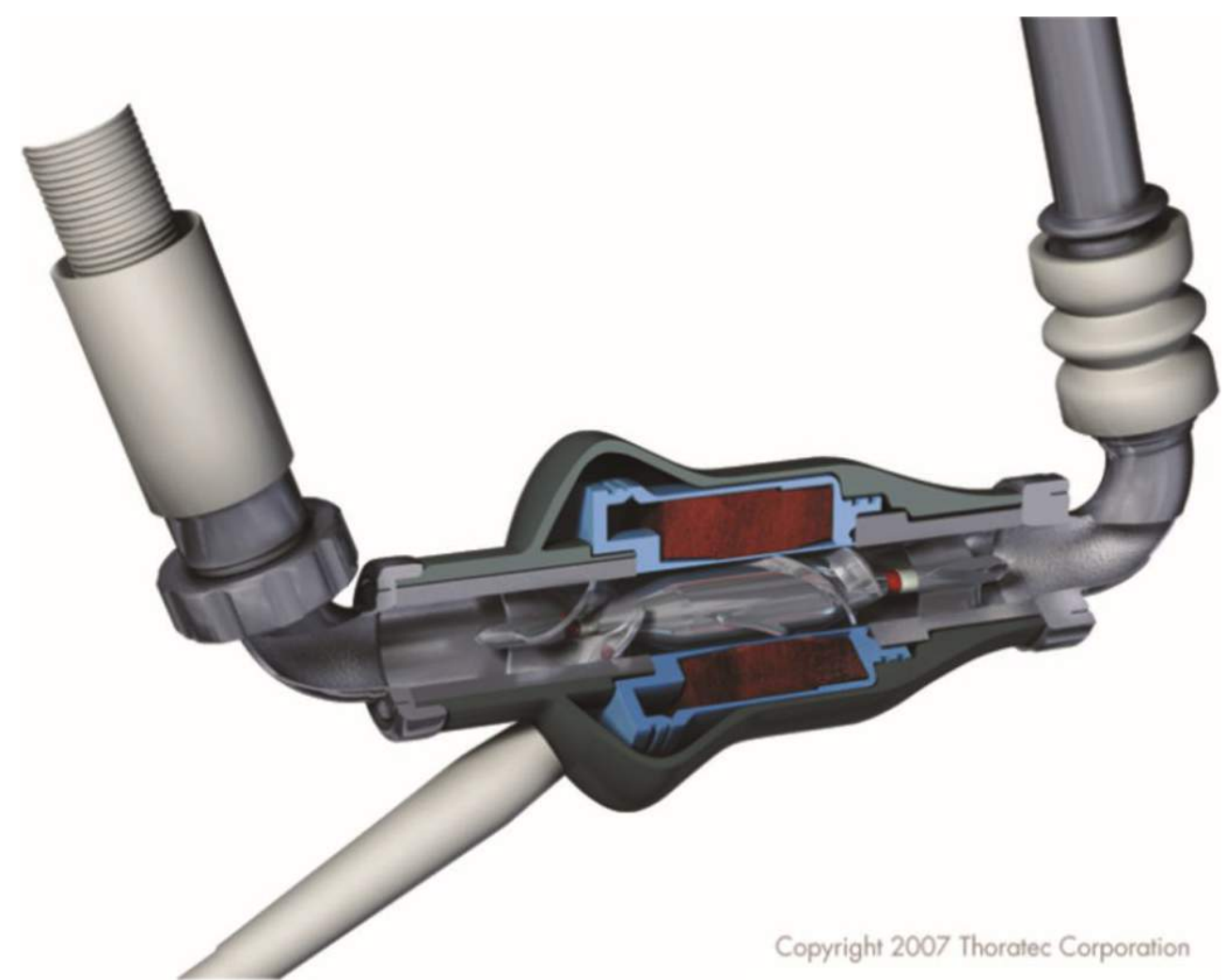


FIGURE 21-1 HeartMate II Cut-Away View. (Reprinted with the permission of Thoratec Corporation.)

Patient Population

The FDA approved the pulsatile Heartmate XVE after the REMATCH (Randomized Evaluation of Mechanical Assistance for the Treatment of Congestive Heart Failure) trial showed improvement of outcomes in patients with severe heart failure who did not qualify for a heart transplant. The Heartmate XVE lacked the durability of current continuous-flow models. Both quality of life and survival at two years were better with the XVE device when compared to the optimum medical management control arm (25% vs. 8%).¹⁵ A subsequent randomized trial comparing the Heartmate XVE pulsatile pump to the HeartMate II continuous-flow pump demonstrated that continuous-flow devices were superior to the pulsatile devices.¹⁶ HeartMate II has been approved for patients without a plan for future transplantation, termed Destination Therapy (DT), as well as patients with a goal of Bridge to Transplant (BTT). Occasionally the devices can function as a Bridge to Cure. These patients are those whose hearts recover and can be weaned from the device. They tend to be younger with a reversible cardiac insult, such as myocarditis or postpartum cardiomyopathy. The goal is to provide the patient's heart time to heal from the temporary insult.

For destination therapy and bridge to transplant, strict inclusion criteria are required. These patients are New York Heart Failure Class IV with resulting impact on their activities of daily living. These patients often require home intravenous inotropics and have evidence of end organ damage from their chronic low flow states with associated high venous pressures and reduced blood pressure. These patients have a high mortality rate with a 1-year survival rate in the REMATCH trial of 18%. Implantation of an LVAD increased the 1-year survival rate to 32%. Coupling this with the high cost of implantation (\$193,812 for implant hospitalization), LVAD utilization has been questioned. A balanced view of this topic has to consider the already enormous cost of treating these patients without implantation. While LVAD management has not reached the definitional cost-effective ratio of \$100,000 per quality adjusted life year (QALY), it has improved and now has been recently estimated to be \$107,569 per QALY for continuous flow pumps.^{17,18}

External Device Paraphernalia

The pumps are implanted either within the thoracic cavity (Heartware) or subdiaphragmatic (HeartMate II). Extending from the pump is a driveline that usually exits the body in the right upper quadrant of the abdomen (infradiaphragmatic). The driveline inserts into the system controller. The system controller houses the circuitry of the device. It incorporates redundancy to improve reliability. Each system controller has a small battery to run the alarms even if power fails. Only the new system controller for Heartmate (Pocket Controller) has a battery capable of driving the pump (~15 minutes of power). If device failure occurs, loud alarms will sound with a flashing red heart in the case of the HeartMate II. Yellow alarms can mean a number of problems, and should prompt an immediate call to the LVAD coordinator.

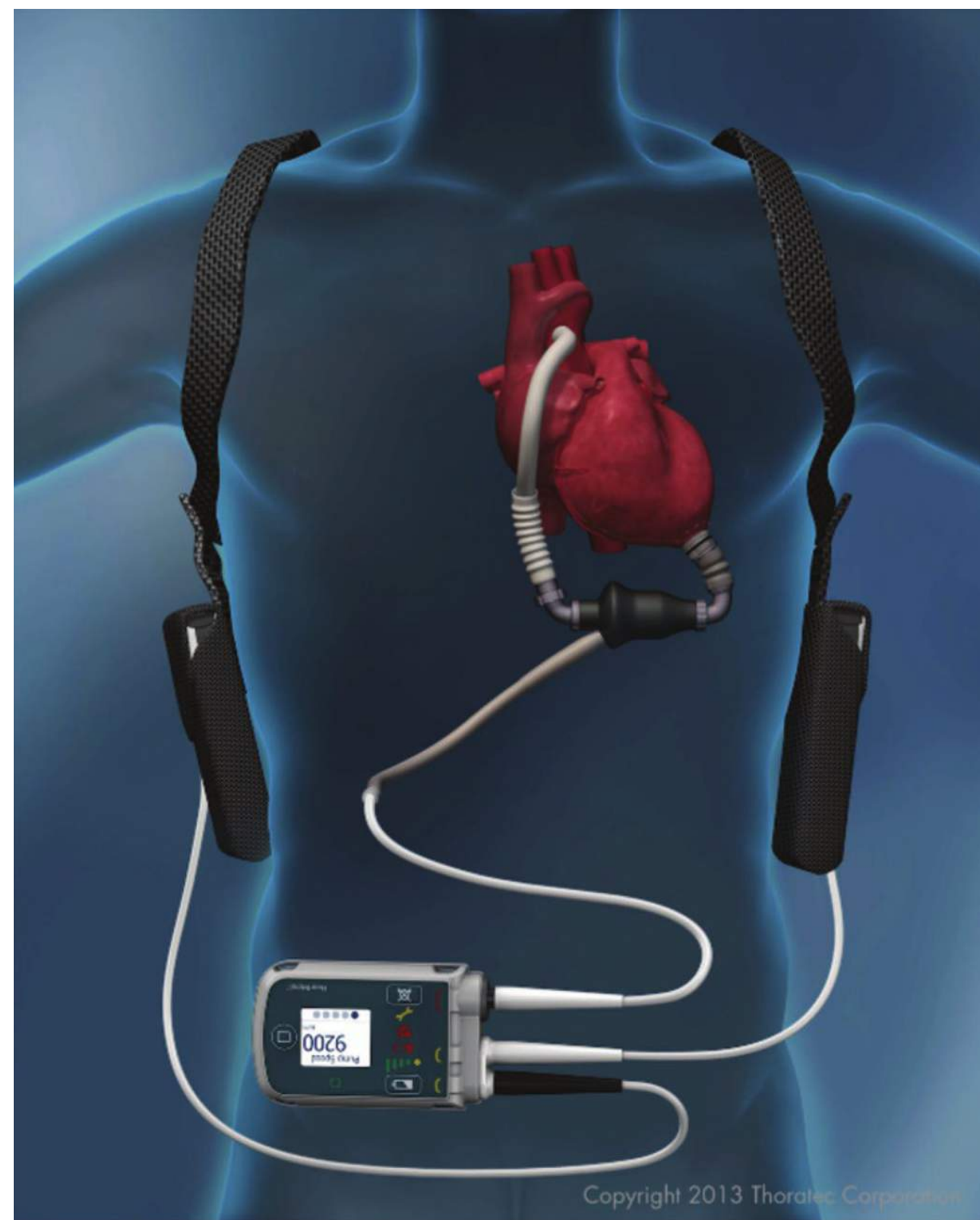


FIGURE 21-2 HeartMate II showing pump connecting into system controller, which connects into two batteries held in a portable vest. (Reprinted with the permission of Thoratec Corporation.)

Two wires connect the system controller to the two external batteries. These can be held in a vest for mobility (Figure 21-2). When the patient is immobile, these wires can be connected to a wall unit called a power-based unit (PBU). The batteries have push-button battery-life panels on the side. This allows for immediate determination of power left in the battery. Changing a battery low on electricity involves removing the battery and replacing it with a charged battery. Obvious problems with loss of pump function occur if both batteries are removed at the same time or erroneously removing the charged battery instead of the empty one. Connecting the patient to the PBU also requires care to ensure that a charge remains with the patient at all times. Battery life for Heartmate lithium batteries is 12 hours.¹⁹

Physiology

LVAD physiology is complex. Juxtaposing a continuous-flow LVAD pump next to the native pulsatile LV creates a temporally changing series of vectors dependent on strength of the native heart, end diastolic LV volume, pump revolutions per minute (RPM), competency of aortic valve, and after-load. Configuring the proper RPM for each patient can be an arduous process, but is fixed for each patient.

Most LVAD patients do not have a palpable pulse. If the native heart function is relatively strong, attenuated pulsatile

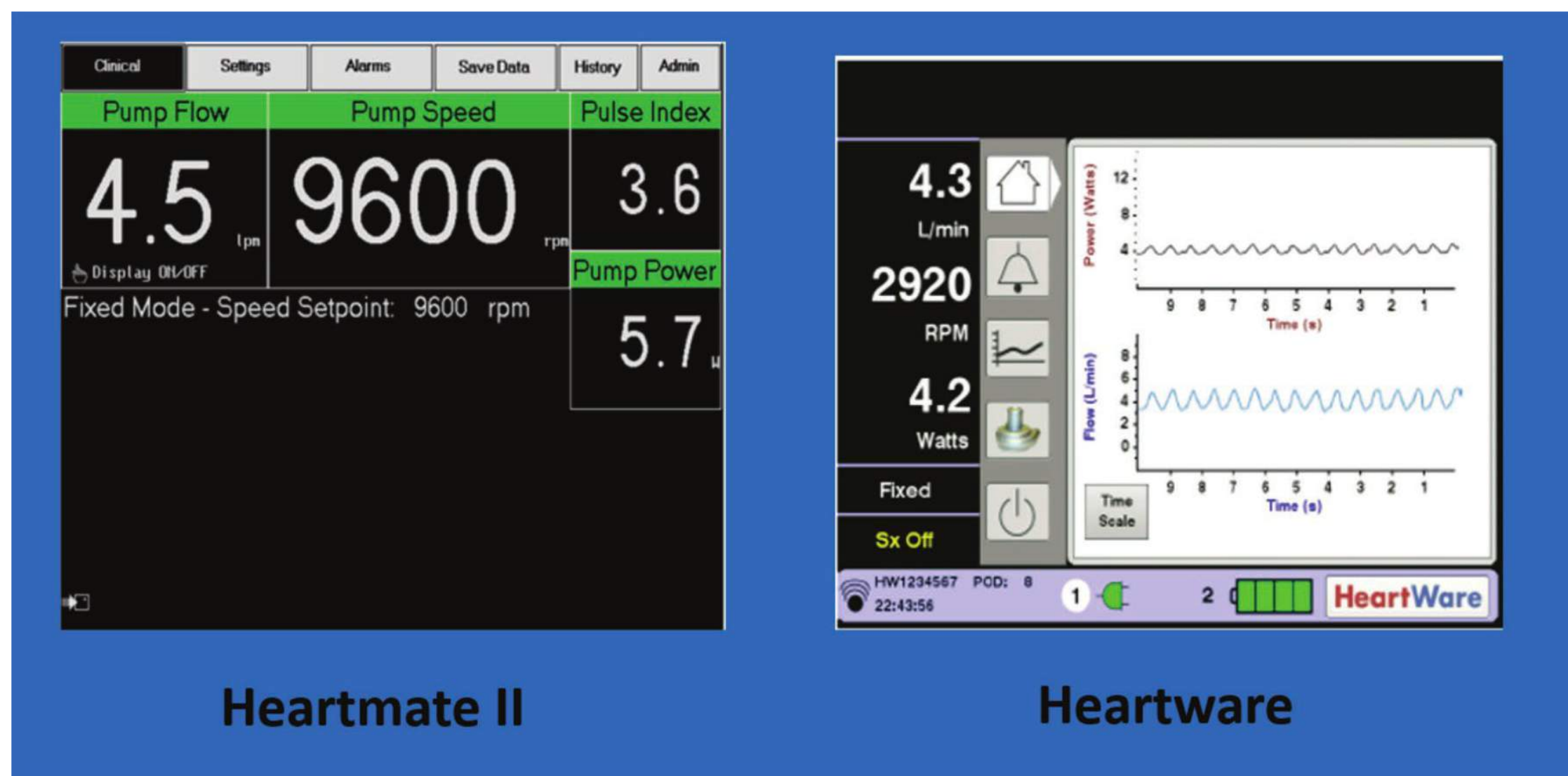


FIGURE 21-3 Display monitor showing pump flow, revolutions per minute (RPM), pulsatility index (PI), and power.

flow through peripheral vasculature can occur. Pulsatility is necessary for standard automatic blood pressure devices to work. These factors make automatic blood pressure measurements often successful even if no palpable pulse can be detected. In patients in which automatic blood pressures are unsuccessful, a manual blood pressure cuff and a Doppler ultrasound can give a mean arterial pressure (MAP). Normal MAP for an LVAD patient is 70 to 90 mm Hg.

When an LVAD patient is plugged into the PBU with a display monitor or with a newer-generation system controller, various parameters can be detected (Figure 21-3). Four main parameters include pump speed (RPMs), blood flow (L/min), pulsatility index, and power (W). The RPMs are usually set to between 8,500 and 10,500 for HeartMate II, whereas Heartware settings are far lower (~2,500 RPMs) (Figure 21-4). Pump speed is set for each patient based on optimal chronic heart function. Intermittent decreases in pump speed can reflect a low-volume state, causing a suction event (described later). Blood flow is a calculated parameter from pump speed and power. This can be highly inaccurate in the acute setting. The pulsatility index gives an idea

how much work the pump is doing compared to the native heart. The pulsatility index (PI) is the average of flows over a 15-second period, calculated by the pump power, normalized to average power. In the HeartMate II, the average PI is 4 to 6, while it is 1 to 8 in the HeartWare VAD. A pulsatility index of less than 2.5 can be an indicator of poor native heart function or low-volume state (Figure 21-5).

Management of Common Problems

LVADs can come to the ED or be admitted to the hospital for any number of reasons. Many problems are LVAD specific. One luxury that should not be overlooked in the management of LVAD patients is the availability of help. LVADs have the advantage that someone knows about them. Often attached to the external controller of the LVAD is the phone number of the patient coordinator on call for that patient. Contact with their facility can help the care provider troubleshoot many problems, give the provider valuable information

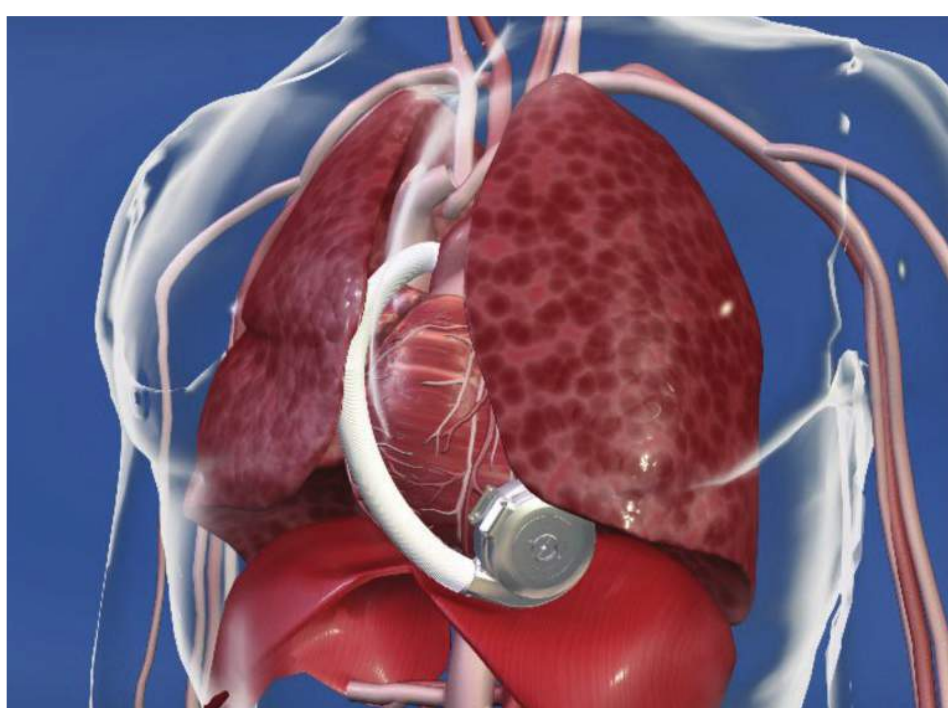


FIGURE 21-4 Heartware in vivo.

LVAD Quick Facts

Normal Parameters

MAP - 70-90

RPMs – 8500-10500 for Heartmate II

~2500 for Heartmate

Pulsatility Index - >2.5 parameters

Red Alarms – Pump malfunctioning

Yellow Alarm – Call LVAD coordinator immediately

FIGURE 21-5 LVAD quick reference.

about the patient, and ultimately provide a place for disposition whether admission or outpatient management is deemed suitable. A good rule for LVAD patients is to never admit them to a facility not well versed in managing LVADs.

GASTROINTESTINAL HEMORRHAGE

Gastrointestinal (GI) bleeding is a common presentation of LVAD patients to EDs. Most patients with LVADs are taking anticoagulants to prevent thrombosis, but even patients not on anticoagulants are at increased risk of bleeding. Shear forces within the pump cause an acquired von Willebrand's deficiency, which is thought to cause bleeding in areas of angiodysplasia and arteriovenous malformations (AVMs). GI hemorrhage can be profuse and emergently life threatening, but commonly is indolent. The indolent ooze that can occur anywhere within the GI tract can be frustrating, with endoscopy/colonoscopy failing to find one culprit. Aggressive reversal with fresh frozen plasma (FFP) is indicated in life-threatening lesions. Prothrombin complexes (PCC) are not well studied in this patient population. Vitamin K is at times avoided secondary to potential need to return a fully anticoagulated state after bleeding is stopped. Management with desmopressin acetate (DDAVP) is possibly beneficial, though understudied.²⁰ Octetride, estrogens, and thalidomide have all been reported to successfully stop GI bleeding in these patients. A gastroenterologist should be consulted, as endoscopy/colonoscopy or wireless pill endoscopy is often necessary. The decision to reverse should be weighed against the risk of stroke or pump thrombosis. Many patients have been managed chronically without anticoagulation if bleeding problems persist.

Trauma in the LVAD patient should be managed similarly to a patient on anticoagulants. A low threshold to image the brain in head injury patients is advised, with observation, repeat imaging, and/or strict return precautions provided for each patient.

VAD-SPECIFIC INFECTIONS

There are three types of VAD-specific infections: driveline infections, pump pocket infections, and VAD-related endocarditis. The LVAD driveline usually exits the body in the right upper quadrant of the abdomen. Having skin flora persistently in contact with a nonorganic substrate is a set-up for infection. Even meticulous care of the site and use of boundary devices can result in a driveline infection. Once an infection occurs, the permanent nidus is difficult to treat. They are particularly problematic because changing a driveline often requires explanting the infected device and implanting an entirely new device. Dilemmas surrounding infection versus colonization occur with cultures taken from driveline areas. CT of the chest and echocardiography are used to determine if an abscess has formed around the driveline. The additional possibility of a pump pocket infection or endocarditis should be considered in the fever of unclear etiology. If a systemic infection is found, broad-spectrum antibiotics are recommended unless a specific pathogen is known.

RIGHT VENTRICULAR FAILURE

At baseline, the right ventricle is often mildly impaired in LVAD recipients. After implantation, the RV output must increase to match the LVAD output. This leads to an increase in RV preload, especially in continuous-flow devices. This increases the demand on the already abnormal RV, leading to worsening RV failure. Also, the leftward shift of the interventricular septum causes worsening tricuspid regurgitation and obstruction of the outflow tract, leading to decreased RV stroke work volume. RV failure (RVF) is associated with increased morbidity and mortality. Common predictors for RVF include increasing right ventricular dilation and tricuspid regurgitation. The failing RV is initially supported with milrinone and dobutamine intravenously. Inhaled nitric oxide and epoprostenol may also be used in the acute setting. Other oral medications used are the PDE5 inhibitors—sildenafil and tadalafil—which act by decreasing pulmonary vascular resistance. If medical therapy alone proves inadequate, mechanical options such as the TandemHeart, Centrimag, and—more recently—the Impella RP, may be required.

AORTIC REGURGITATION

High-velocity flow through the ascending aorta results in increased wall stress and compensatory thinning of the aortic media layer. This may lead to aortic root dilatation and subsequent aortic regurgitation.²¹ Also, if aortic opening does not occur, the closed valve is subjected to high systolic pressures, which leads to structural remodeling and commissural fusion of the valve. In the case of severe regurgitation, the LVAD output decreases. Mild–moderate aortic regurgitation is managed by adjusting the pump speed of the continuous-flow device to decrease the outflow cannula velocity and simultaneously allowing for opening of the aortic valve to a ratio of 1:3 cardiac cycles. Severe cases require aortic valve replacement (AVR), patch closure of the aortic root, or aortic valve closure.

Management of LVAD in Extremis

Determining whether an LVAD patient is in cardiac arrest is far more complicated than for a traditional patient. Thus, the term *LVAD in extremis* is used to alleviate the confusion around true cardiac arrest versus simply altered mental status. An algorithmic approach to the LVAD patient in extremis is advised (Figure 21-6). An LVAD patient with altered mental status should be considered in extremis until proven otherwise. Unlike most patients, in whom simple detection of a central pulse can diverge you from the cardiac arrest pathway, LVADs rarely have a palpable pulse. This, coupled with the reliance of most LVAD patients on a functioning pump, make determination of the pump's status of utmost importance.

Depending on the clinical scenario, planning for an LVAD arrest is key. If the institution is an LVAD receiving center, then preparations should be made for how to rapidly obtain PBU and practitioners trained in LVADs. If the institution is not an LVAD center, then physician and nurse education, along with a purchase of a PBU, may be prudent.

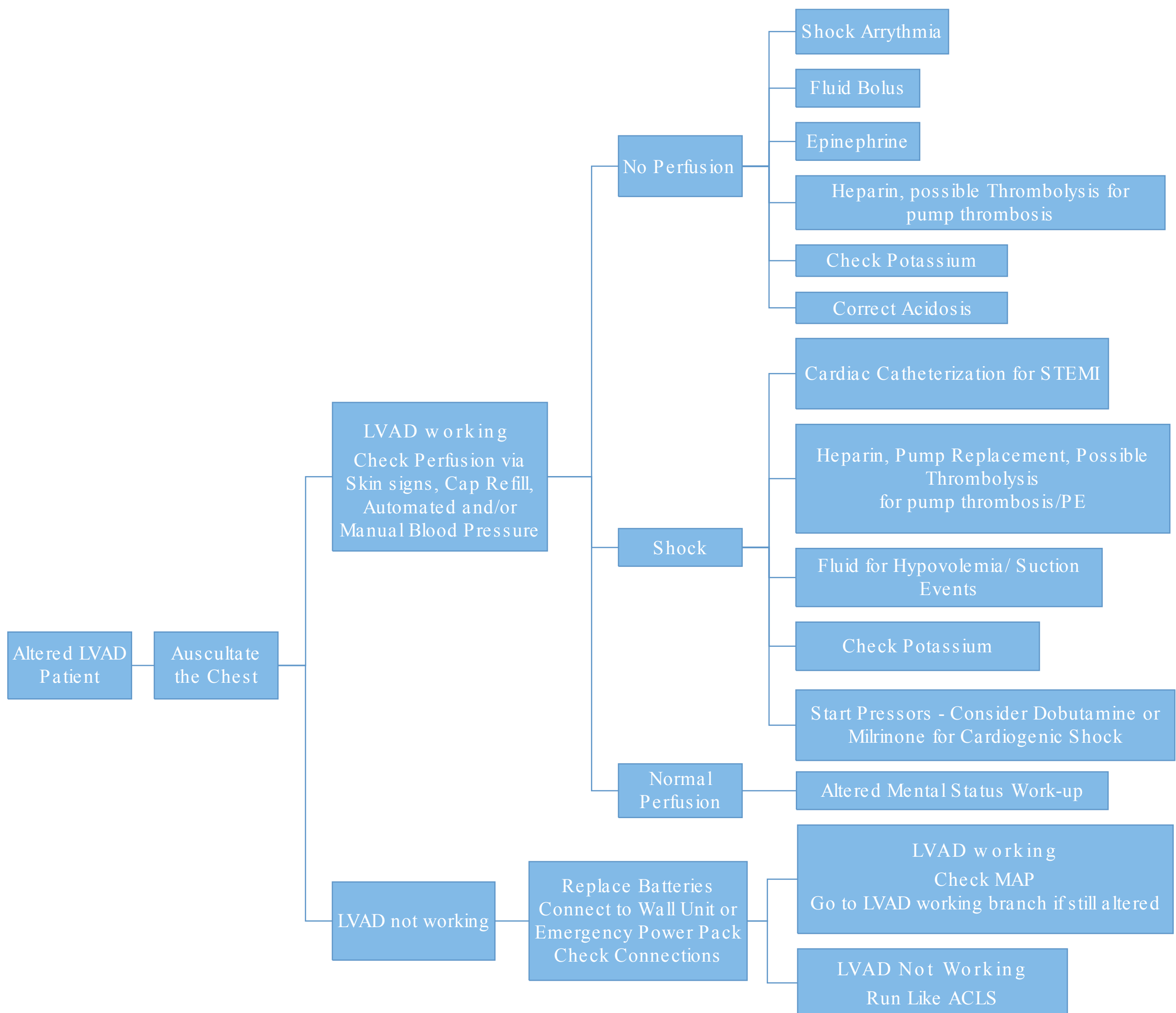


FIGURE 21-6 Management of LVAD in extremis.

In addition to planning for an LVAD arrest, prehospital care of the LVAD patient can save lives. Loss of power is a common cause of sudden cardiac arrest.²² If power is a likely cause of arrest, the prehospital personnel should be directed to find and connect the extra batteries that all LVAD patients should be carrying. If this is in the patient's home, then the wall unit should be used to restore power to the patient. Patients should also have an Emergency Power Pack (EPP), which can be used for supplemental power. Transporting a patient with a nonfunctioning LVAD is often not in that patient's best interest. Every attempt should be made to restore power at the scene. In contrast, pronouncement of an LVAD patient in the field is not advised. Transport to a hospital for thorough evaluation should be made.

The initial step in assessment of the LVAD in extremis is to auscultate the chest. This is the fastest way to assess whether the pump is working. If the “hum” of the motor is

auscultated, then you know electricity is getting to the pump. If the pump is not working, then the priority of the resuscitation will be to troubleshoot the LVAD. This will be described in greater detail later (Figure 21-7).

THE PUMP IS WORKING

If the pump is working, then the next step is to determine perfusion. Initially, an automated blood pressure cuff should be used to assess blood pressure. Secondary signs of perfusion—such as capillary refill, skin color, and temperature—should be evaluated. If the automated blood pressure cuff does not detect a blood pressure, a manual blood pressure cuff using Doppler is recommended. Even with brief resuscitations, an arterial line insertion should be considered since accurate knowledge of postresuscitation hemodynamics are imperative and can be difficult to quickly determine otherwise.

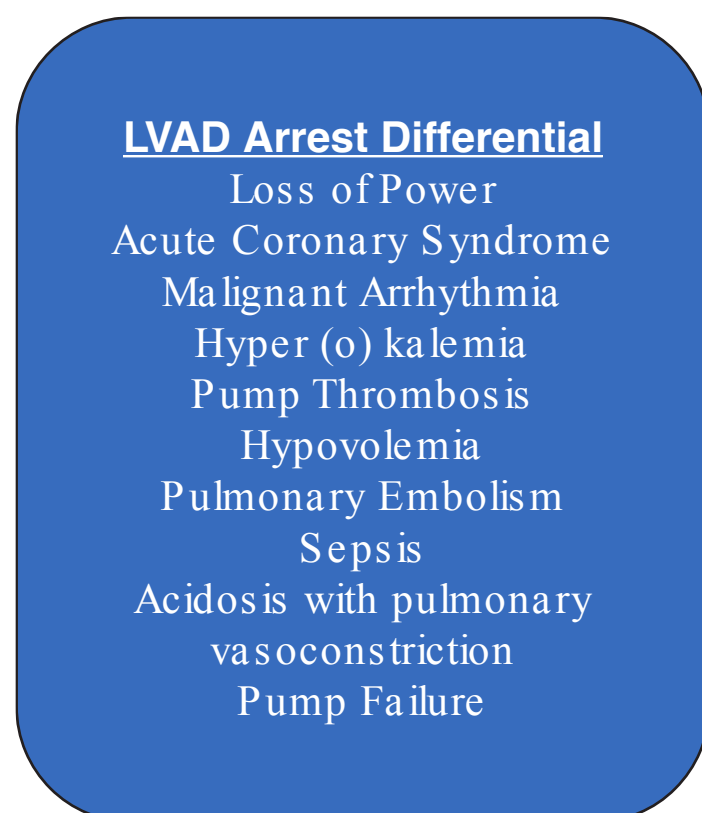


FIGURE 21-7 LVAD arrest differential diagnosis.

SHOCK: HYPOVOLEMIC

If the blood pressure is low ($\text{MAP} < 60$), then determination of the cause of shock is necessary. Causes of shock are predominantly the same as those of non-LVAD patients. Consideration of volume status is important. Diuretic use is common in the LVAD population; dehydration can have problematic effects on the pump. Because the pump is set at a fixed RPM, it will pull blood from the left ventricle regardless of the volume status of the ventricle. In low-volume states, this pull can actually result in removal of more blood than is returned to ventricle via the pulmonary system. This will cause the side walls of the ventricle to collapse on each other, resulting in a “suction event.” An untreated suction event will result in cardiovascular collapse secondary to no flow into or out of the left ventricle. The LVAD circuitry can detect this phenomenon and will automatically drop the RPMs down to a preset level. This will allow more volume to enter the left ventricle and open the ventricular walls. The LVAD will then slowly increase its RPMs back to the set value. If persistent low volumes occur, then another suction event will occur. Recognizing recurrent suction events can be difficult but suggest low-volume states. Listening to the device can provide clues, as one will hear the pitch change associated with the decrease in RPMs and the subsequent rise in pitch back to the previous set value for RPMs.

Beyond the difficulties of detecting suction events, determining volume status of an LVAD patient is problematic. Usual clues—such as mucous membrane moisture, capillary refill, urine output, and heart rate—can be used. An additional clue is the pulsatility index. This number is used as a surrogate of percentage of flow generated by the native heart. Decreases in the pulsatility index may also reflect in a decrease left ventricular volume and, therefore, volume status.

SHOCK: CARDIOGENIC

Cardiogenic shock is also common. While increased left ventricular failure can often be overcome by the pump, right ventricular failure can result in significant decreases in cardiac output. The right ventricle is responsible for pushing blood through the pulmonary system and subsequently left

ventricular end diastolic volume. Right ventricular myocardial infarction/ischemia can cause this, and should be treated similar to patients without an LVAD. Cardiac catheterization is advisable. Common pressors in LVAD cardiogenic shock include milrinone and dobutamine. Another cause of cardiogenic shock is arrhythmias. Ventricular fibrillation (Vfib) and tachycardia (Vtach) can be defibrillated in LVAD patients. Care should be taken to not put the defibrillator pads directly over the device since that might divert the electrical current through the device and avoid the arrhythmic heart. LVAD patients often have automatic implantable cardioverter defibrillators (AICD)/pacemakers implanted; thus, malignant arrhythmias may have already had attempted internal defibrillation. Also, of note, the pacemaker function is usually around 90 beats per minute in hopes of improving right ventricular output.

LVAD patients with arrhythmias and myocardial infarction are often critically ill. There are many examples of LVAD patients with these types of pathologies being unaware of their state. There have been LVAD patients in ventricular fibrillation who have driven themselves to our hospital. The effect of these conditions on the patient state are directly related to the pulmonary vascular resistance (PVR) and volume status. In typical heart failure patients and patients recently implanted with an LVAD, PVR remains elevated as the patient’s physiology gradually adjusts to the newly lowered left atrial pressure. As time from implantation increases, the PVR decreases. A low PVR facilitates LVAD filling as long as the central venous pressure is high enough to provide an adequate transpulmonary flow. A low PVR allows the LVAD to draw blood through the pulmonary system with less dependence on the right ventricular native heart contribution. Liberal use of myocardial markers, cardiac monitoring, and electrocardiograms in these patients is warranted.

In addition to arrhythmia and myocardial dysfunction, shock can be caused by valve dysfunction. Because the outlet cannula of the LVAD is placed in the proximal ascending aorta, aortic valve leaflets experience increased constant diastolic loading. This creates varying degrees of aortic insufficiency (AI) in up to 77% of patients by postimplantation year 1.²³ The severity of this problem can range from outpatient follow-up to true emergency. In the latter situation, the pump will show normal or high flow parameters with persistent hypotension peripherally. Effectively, the pump is pushing blood through a closed circuit. This circuit consists of blood traveling retrograde through the aortic valve back into the left ventricle, then into the inlet valve of the cannula. Severe AI in LVAD patients can present as pulmonary edema and right heart failure with elevated left heart filling pressures. This can be a surgical emergency, for which immediate consultation with a cardiovascular surgeon is indicated. Emergent transthoracic echocardiogram is advised.

SHOCK: DISTRIBUTIVE

Distributive shock in the form of sepsis is also common in the LVAD population. Driveline infections are certainly novel causes of sepsis, but common forms of sepsis predominate.

Pneumonia, urinary tract infections, and so on should be checked and broad spectrum antibiotics used if no specific source is found. Vasopressors such as levophed or phenylephrine should be considered to augment peripheral vasoconstriction to and to ensure adequate right heart coronary artery perfusion pressure.

PUMP MALFUNCTION

Shock can also be caused by a working pump that is not providing adequate flow. The most common example of this is pump thrombosis. A pump that is thrombosed will present with decreased flows through the pump despite increased work by the pump. Reliance on the flow monitor accompanying the pump can be deceiving since these values are calculated from current drainage data. One clue to this will be a hot system controller. As the pump increases its attempt to spin, the electricity through the system controller will increase, resulting in a controller that is hot to the touch. For patients with pump thrombosis who have been taken off anticoagulation, the risk/benefit on restarting will need to be weighed. In some patients, thrombolysis with tissue plasminogen activator (TPA) should be considered; however, results to date have been best with pump replacement. Discussion with an LVAD coordinator and cardiothoracic surgeon is advised if time allows.

CARDIAC ARREST IN THE WORKING LVAD

Determination of cardiac arrest in an LVAD patient is more difficult than in a normal patient. After auscultating a working pump in an altered LVAD patient, quickly determining perfusion is paramount. The use of automated blood pressure machines is unreliable and obtaining a manual blood pressure cuff may take time. Use of secondary signs of perfusion—such as capillary refill, skin color, and temperature—are useful. Use of bedside cardiac echo can be helpful, as it may show decreased or lack of cardiac activity. Cardiac monitoring with signs of ventricular arrhythmia may also be a clue. Quick information gathering via these sources can allow rapid determination of cardiac arrest. Within this context though, the practitioner must be aware of other causes of altered mental status. Blood sugar and potassium determination should be added to the initial assessment and consideration for seizure, encephalitis, and toxic and metabolic causes of altered mental status.

Once determination of cardiac arrest has occurred, specific interventions for the cause of the arrest should be employed. In general, therapy during an arrest is directed at maintaining right ventricular output since LVAD flows are entirely dependent on receiving blood from the lungs. Acidosis is corrected since it serves as powerful pulmonary vasoconstrictor, especially in LVAD patients whose pulmonary vascular bed remains potentiated from chronic heart failure. In some cases, administration of inhaled nitric oxide can be lifesaving. MAP is kept elevated to maintain right coronary perfusion and prevent right ventricular ischemia, which can occur when the difference between MAP and central venous pressure (CVP)

is < 40 mm Hg. Inotropic agents that reduce PVR, such as dobutamine and milrinone, are used to enhance RV contractility. Any systemic vasodilatory consequences are counteracted by using systemic vasoconstrictors, such as vasopressin or levophed. Defibrillation for arrhythmias should be done. Special consideration for hyperkalemia or hypokalemia should be taken, as LVAD patients are often on diuretics with supplemental potassium. Alterations in renal function has offset this balance and creates either an excess or deficiency of the intravascular potassium. Typical measures—including sodium bicarbonate, calcium chloride/gluconate, albuterol, and insulin/glucose—can be used.

CARDIAC ARREST: EPINEPHRINE

Use of intravenous epinephrine in cardiac arrest is controversial outside of the LVAD population; this same controversy exists within this population. Keeping in mind the potential downside of getting return of spontaneous circulation (ROSC) without the return of neurologic function (RONF) with use of epinephrine, there is no contraindication to administration of 1 mg of epinephrine every 3 to 5 minutes.

An important point in the treatment of an LVAD with a working pump is that the pump affords a great deal of aid in restoration of effective circulation. To avoid the confusion associated with the term spontaneous circulation, use of return of effective circulation (ROEC) is advised. ROEC is therefore possible in patients with LVADs that may not have been possible in a normal patient. Administration of a bolus of intravenous saline may be effective enough to restore circulation by allowing the pump to effectively distribute the blood volume. A useful analogy is the following: an LVAD patient with a working pump is like having a patient on extracorporeal membrane oxygenation (ECMO).

CARDIAC ARREST: CHEST COMPRESSIONS

One of the most controversial areas of LVAD resuscitation is use of manual chest compressions. Most institutions have recommended against their use in these patients for fear that the trauma from compression would dislodge the pump. With older, larger LVAD models, this may have been more likely. With current models, this is unclear. Regardless, use of chest compressions within this population involves more risk than normal patients. This increased risk is coupled with the difficult task of determining whether a patient is in cardiac arrest. This creates the chance that a potentially harmful therapy would be applied to a patient population not in need of it. Understandably, many cardiothoracic surgeons recommend against its use.

This risk, however, must be weighed against the risk of not performing the intervention on the patient. A patient in cardiac arrest certainly has a high risk of morbidity and mortality. Use of bystander chest compressions in non-LVAD patients has been associated with substantial improvements in survival.²⁴ Our institution has been unique in that we have believed that chest compressions should be done in the LVAD population. We published a small case series showing

no dislodgement of the pump in 8 patients who received chest compressions. There are no studies or case reports, to our knowledge, of patients having dislodgement of the pump with current-generation LVAD pumps. Our series also showed that 4 of the 8 patients were neurologically intact survivors of their arrest.²²

Saying that chest compressions are possibly safe and effective in the LVAD population understates the complexity associated with this patient population. With a working pump, the heart may only need to transfer blood from the right atrium through the pulmonary vasculature to the left ventricle. In a cardiac pump model for chest compression mechanism, this would suggest that only compression of the right ventricle is necessary to restore effective circulation to the body. This could mean that chest compression depth could be decreased to simply compress the RV. A number of problems exist with this description. While the idea that compression of the heart (cardiac pump model) produces flow is true, increases and decreases in intrathoracic pressure (thoracic pump model) is likely the predominant determinant of blood flow during chest compressions. Secondly, partial compression of the chest may not compress the right ventricle enough to produce effective flow. Understanding these two limitations, a modified chest compression technique involving less emphasis on the full 5 centimeters of compression is reasonable in a patient with a functioning pump.

THE PUMP IS NOT WORKING

If auscultation of the LVAD patient in extremis reveals no motor sounds, then every attempt to get the LVAD working should be employed. In our case series of 8 patients, 5 of the patients' cardiac arrests were due to accidental disconnect. This means that the patients were changing their batteries or forgot to change their batteries and their pump ran out of electricity. Familiarizing yourself with the external components of the LVAD is critical to improving the survival of your LVAD patients. Each system is different; thus, hands-on knowledge in this area should be emphasized.

If the pump is not working, then the practitioner should systematically find why it is not working. It is likely that the device's alarm will be going off, with a red heart flashing on the system controller for the HeartMate II device (see earlier Paraphernalia section). This alarm will stop if the battery and system controller is completely out of electricity. If possible, retrieval of the PBU for the specific device should be made prior to arrival of the patient. Upon arrival, the patient should be immediately plugged into the PBU. If no PBU is available, the practitioner should evaluate the two batteries held in a vest on the patient. On the side of the batteries are push buttons that will tell how much electricity is left in each battery. If no electricity is left, then search the patient's belongings for extra batteries.

If even one battery has electricity left, the pump should function. If the pump is not functioning, then undo and reconnect the batteries to the system controller. If this is unsuccessful, then exchanging the system controller for a new one is advised. Failure to restore the pump function after

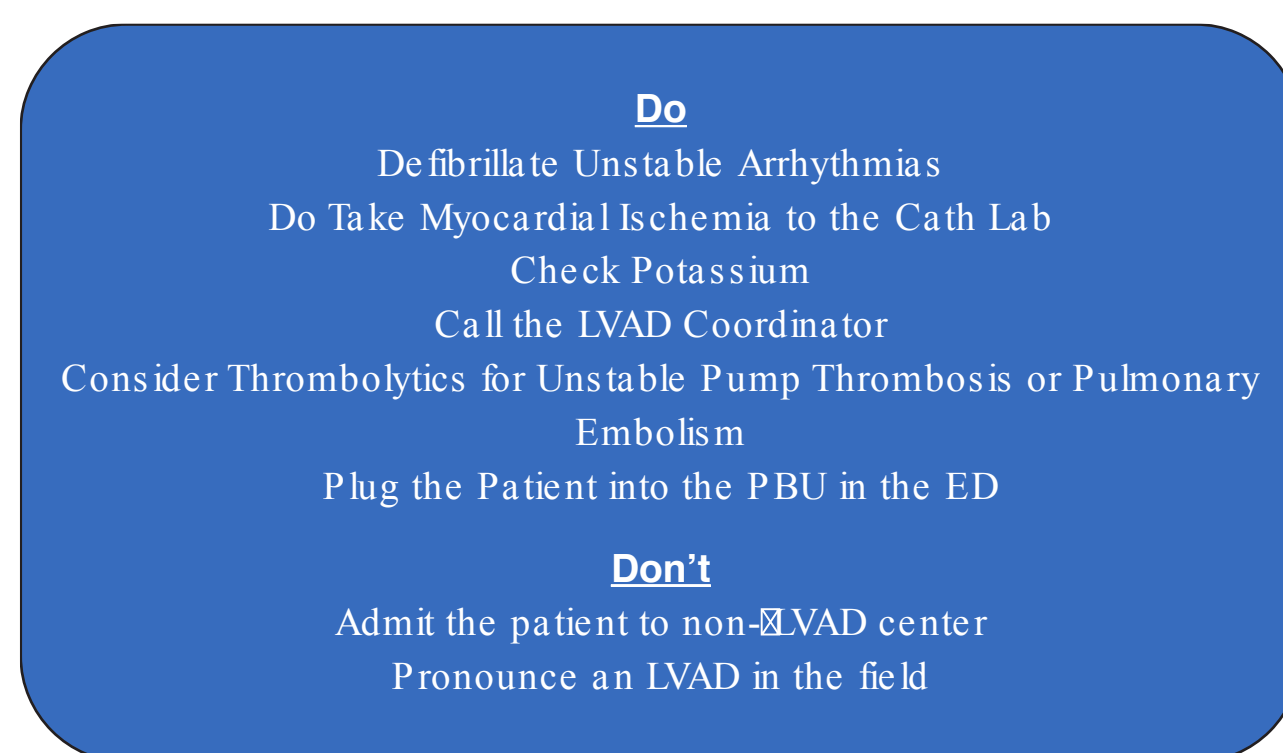


FIGURE 21-8 Do's/Don'ts of LVAD.

this may prove futile. Pump malfunction secondary to system controller malfunction, wiring failure, or intrinsic mechanical pump failure often results in death of the patient.

As stated, every effort should be made to restore function of the LVAD in an arresting patient. If function cannot be restored, then following usual algorithms for cardiac arrest are prudent. Defibrillation can be done, keeping the path of electricity away from the pump. Epinephrine can be given. Chest compressions are controversial. As stated earlier, the fear of dislodgement has caused many to recommend against the use of chest compressions. In an arresting patient with a nonfunctioning pump, the prognosis is extremely grave and use of chest compressions may be warranted (Figure 21-8).

CONCLUSIONS

Patients with LVADs are complex. They require planning on the part of the hospital to prepare for the possibility of everything from a cardiac arrest to an ankle sprain. Having trained personnel (nurses, technicians, and physicians) and equipment readily available is key. Patients requiring admission should be transferred to centers experienced at managing LVADs. The key to restoration of effective circulation in an arresting LVAD patient begins with fixing a malfunctioning pump.

Special thanks to Walter Dembitsky, Peter Hoagland, Marcia Stahovich, and Suzanne Chillcott for their help in writing this.

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Pericardial Diseases

Joseph R. Shiber

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INTRODUCTION

In the 16th century, Vesalius first described the anatomy of the pericardium. In 1674, John Mayow gave the earliest account of constrictive pericarditis: “the heart was nearly covered by cartilage, adherent to its interior so that blood could scarcely enter.” Richard Lower accurately described tamponade in 1689: “a profuse effusion oppresses and inundates the heart. The walls of the heart are so compressed by the fluid circling everywhere, so that the heart cannot dilate sufficiently to receive the blood, then the pulse becomes exceedingly small, thence succeed syncope and death itself.”¹ Franz Schuh did the first successful pericardiocentesis in 1840; Churchill performed the first pericardiectomy in the United States in 1929. Claude Beck described his triad of findings in tamponade in 1935. In 1954, Edler demonstrated a pericardial effusion by ultrasound, and in 1971 Spodick described the EKG findings associated with pericarditis.^{1,2}

ANATOMY AND FUNCTION

The pericardial sac is formed by the visceral and parietal pericardium, which are continuous with one another at the attachment of the great vessels (Figure 22-1). The visceral component is a single mesothelial cell layer with a submesothelium that is invested directly against the myocardium. The visceral pericardium forms the pericardial fluid, an ultrafiltrate of the plasma, normally 20 to 50 cm³, which is then drained via the parietal pericardium to the thoracic duct. The parietal component is approximately 1 mm thick and formed of three layers: (1) *serosa* of mesothelium; (2) *fibrosa* of dense, wavy collagen fibers and interspersed elastic fibers, also containing fibroblasts, mast cells, nerves, blood vessels, and lymphatics; and (3) *epipericardium* of collagen, elastin,

and adipose. It is this third layer that forms the ligaments inferiorly to the diaphragm, superiorly to the deep cervical fascia, anteriorly to the manubrium and sternum, and posteriorly to the vertebral column.^{3–5}

Although there are many recognized functions of the pericardium, its removal or congenital absence is well tolerated except for partial defects that can lead to cardiac herniation. The tensile strength of the pericardium is greater than the myocardium, and it retracts when incised, suggesting that it is under tension. The pericardium maintains the heart in proper position, acts as a barrier to infection, and prevents overdilation of the chambers in response to hypervolemia. It is devoid of impulse-generating capacity; thus, it does not produce any EKG deflections.⁵

Intrapericardial pressure approximates pleural pressure, varying with respiration to aid in venous return and atrial filling. The tension of the pericardium evenly distributes the pericardial fluid against the heart, allowing the pericardial fluid to decrease friction, disperse gravitational and inertial forces around the heart, and distribute hydrostatic forces, giving uniform stretch of myofibrils to allow *Frank–Starling* mechanics to operate over a range of pressures.

Together, the pericardium, circumferential myocardial fibers, and a compliant septum allow for ventricular interdependence. This mechanism mostly affects diastolic interactions and balances output from both ventricles over several cycles based on the volume–pressure relationship. As the pressure in one chamber increases (due to volume filling), the compliance of the other ventricle decreases (restricting filling). The increase in right-heart filling with inspiration (negative intrapericardial pressure and increased venous return, with increased pulmonary vascular capacity) is evidenced by increased tricuspid and pulmonic valve flow velocities, as well as simultaneous decreased left-heart filling and mitral and

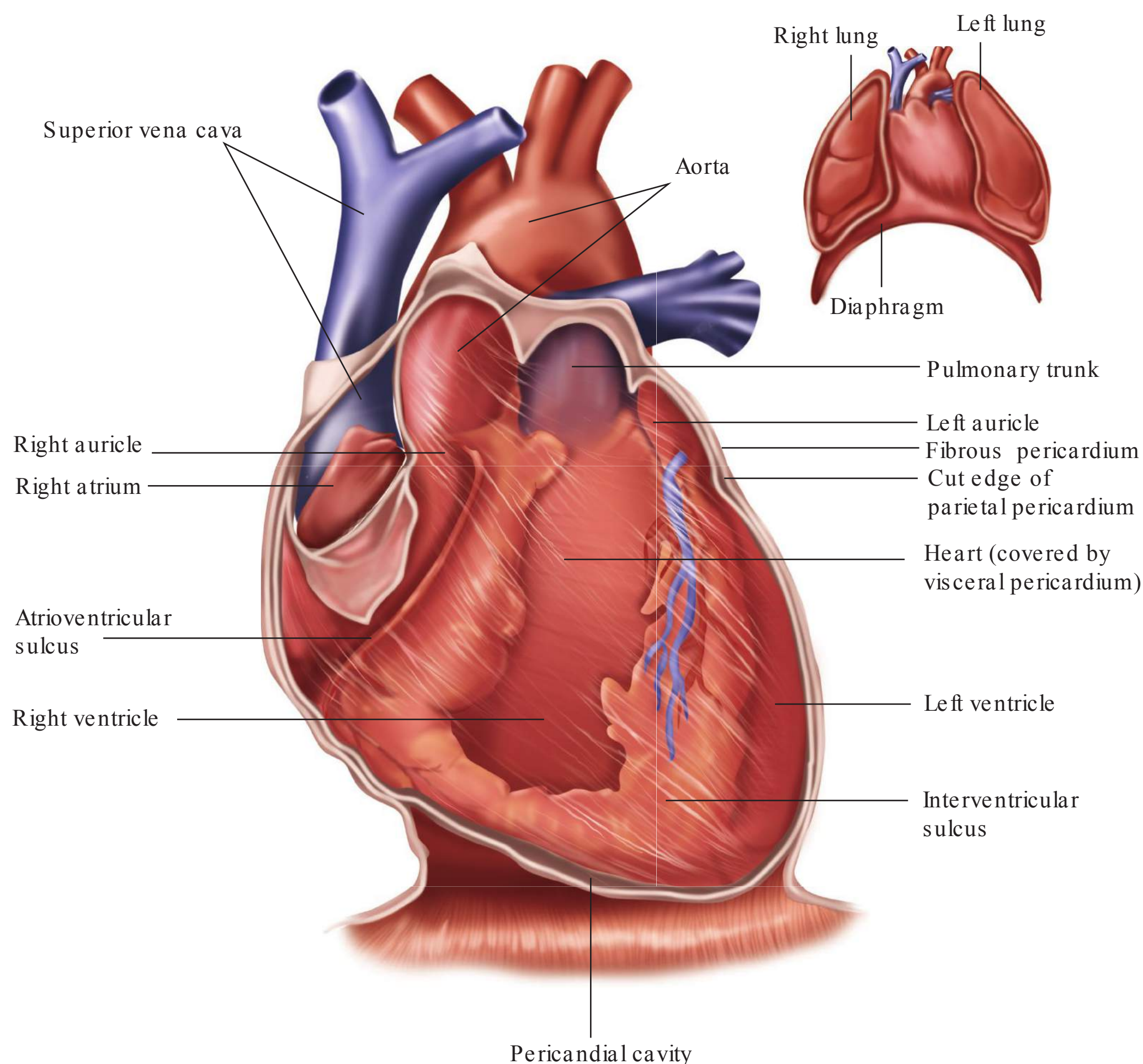


FIGURE 22-1 Image of the heart demonstrating the layers of pericardium making up the pericardial cavity, and covering the roots of the great vessels. (Reproduced with permission from Sickles NA, Lewis R, Butler J, et al: *Hole's Human Anatomy and Physiology*, 7th edition. TM Higher Education Group Inc; 1996.)

aortic valve flow velocities. The opposite dynamics occur with expiration, and these volume–pressure effects are exaggerated by hypervolemia and minimized by hypovolemia.^{3–5}

Pericardial Appearance on Cardiac Imaging

The normal pericardium is typically not directly visualized by echocardiography, but instead shows as an echogenic bright line at the interface with lung tissue. Only if the pericardium is significantly thickened (> 5 mm) will it be directly visualized by echocardiography. On cardiac CT (CCT) the normal pericardium averages 1.3 to 2.5 mm in thickness and is seen as a bright linear structure with or without intravenous contrast. It is best imaged in systole but visibility can be difficult in the region of the lateral, posterior, and inferior left ventricle due to decreased pericardial fat. On cardiac MR (CMR), the pericardium is normally seen as a low-signal-intensity structure on electrocardiographic-gated T_1 -weighted sequences. Similar to CCT, visualization of the pericardium is dependent on the amount of epicardial fat.⁶

PATHOPHYSIOLOGY

Pericardial diseases include pericarditis, constriction, and congenital or traumatic pericardial lesions. Although the etiologies for pericarditis are numerous (Table 22-1), the initiating factors for inflammation and effusion are shared; any of these factors, if chronic, can eventually cause pericardial constriction.^{4,7}

There are three stages to pericardial inflammation: (1) vasodilation leading to transudation of a protein-poor, cell-free fluid; (2) increased vascular permeability allowing protein (fibrin) to leak; and (3) inflammatory cell migration. The presenting complaint is usually substernal chest pain, radiating to the left, or both, scapular ridges since innervation of these muscles is via the phrenic nerve that crosses the pericardium.⁸ It is classically pleuritic and positional, often being relieved by leaning forward. As an effusion develops, symptoms from compression of adjacent structures (trachea, esophagus, phrenic nerve, and recurrent laryngeal nerve) include dyspnea, cough, dysphagia, singultus, and dysphonia.^{3,5,7} Although there are no formal diagnostic criteria for


TABLE 22-1: Common Categories of Pericardial Disease
Idiopathic
Infectious

Viral, bacterial, mycobacterial, fungal

Autoreactive

Lupus, rheumatoid arthritis, scleroderma, vasculitis, post-MI, drug induced

Neoplastic

Lung, breast, lymphoma, melanoma, mesothelioma

Metabolic

Renal failure, hemodialysis, myxedema

Traumatic

Cardiac injury (penetrating or blunt), iatrogenic (catheterization, pacer lead, venous line), radiation

Contiguous disease

Aortic dissection, ventricular aneurysm/rupture, pulmonary/pleural disease

acute pericarditis and it mostly remains a clinical diagnosis, it has been suggested that at least two of the following four criteria should be present: (1) characteristic chest pain, (2) pericardial friction rub, (3) typical EKG changes, and (4) new or enlarged pericardial effusion. High-risk features that may indicate a complicated course include fever $> 38^{\circ}\text{C}$, leukocytosis, a large effusion (> 2 cm), acute chest trauma, immunosuppressed status, anticoagulation therapy, failure of NSAID therapy, and recurrent pericardial disease.⁸

Patients with pericarditis have systemic evidence of inflammation on blood testing, including a leukocytosis and elevated C-reactive protein level and erythrocyte sedimentation rate. Troponin levels are elevated in 35% to 50% of pericarditis cases (creatine kinase-MB fraction less often) due to epicardial inflammation, and typically return to baseline within 1 to 2 weeks. The magnitude of the troponin rise appears to correlate with the height of the ST-segment elevation, but does not necessarily predict an adverse outcome. Serum troponin levels remaining elevated for more than 2 weeks suggest an associated myocarditis, which predicts a worse prognosis.^{7,9} The initial workup and management for any patient with presumed pericarditis should be: (1) an evaluation for possible underlying or causative conditions; (2) echocardiography to determine if there is an effusion (and, if so, its size), tamponade, or other structural abnormalities; (3) alleviation of symptoms with anti-inflammatory medications; and (4) treatment for a specific condition, if identified.^{4,5,9}

Infectious Pericarditis

Viral agents are the most common cause of pericarditis, as documented by rising antibody titers, but also represent the majority of cases thought to be idiopathic (Table 22-2). Enteroviridae (Coxsackie B), Adenoviridae, Echoviridae, and Retroviridae are usually responsible, and pericardial involvement typically occurs 1 to 3 weeks following a upper


TABLE 22-2: Microbiology of Infectious Pericarditis
Viral

HIV

Coxsackievirus A and B

Epstein–Barr virus

Echovirus

Influenza

Paramyxovirus (mumps)

Adenovirus

Varicella

Bacterial

Staphylococcus

Streptococcus

Pneumococcus

Gram-negative bacilli

Meningococcus

Gonococcus

Haemophilus influenzae

Bordetella pertussis

Francisella tularensis

Salmonella

Campylobacter

Listeria

Legionella

Mycoplasma

Nocardia

Actinomyces

Anaerobic

Clostridium

Peptostreptococcus

Rickettsial

Typhus

Q fever

Fungal

Histoplasma

Candida

Coccidioides

Blastomyces

Aspergillus

Protozoal

Toxoplasma gondii

Entamoeba

Trypanosoma cruzi

Parasitic

Trichinella

Filarioidea (microfilaria)

Echinococcus

Mycobacterial

Tuberculosis

Avium-intracellulare complex

respiratory infection (URI) or gastrointestinal (GI) infection, although rarely pericarditis can occur with the primary infection. Viral pericarditis is typically “dry”—without a pericardial effusion—with a rub present, or may develop a small effusion that is asymptomatic and resolves spontaneously.^{5,9,10}

Although atrial arrhythmias can be seen, mostly with constrictive disease, patients with uncomplicated pericarditis predominantly remain in sinus rhythm and have no significant arrhythmias. When arrhythmias occur, underlying conductive disease or an associated myocarditis is usually responsible and should be sought. The classic example is Lyme pericarditis, which is really a pancarditis that can cause a bundle branch or A-V nodal block.^{3,11}

BACTERIAL

In the preantibiotic era, purulent pericarditis resulted in a nearly 100% mortality rate. Unfortunately, today it still carries a high mortality rate (30%–50%) since affected patients typically have severe underlying medical disease. Bacterial pericarditis is not a primary infection, but is almost exclusively a complication from an underlying infection.^{12,13} In one study, 13% of the cases of purulent pericarditis (confirmed by pericardial fluid analysis or at autopsy) were found in patients admitted to the ICU with a diagnosis of sepsis.¹⁴ Risk factors include advanced age, diabetes mellitus, untreated infection (pneumonia), extensive burns, an immunosuppressed state, and a preexisting pericardial effusion (renal failure, congestive heart failure). The physician must maintain a high index of suspicion in patients with a septic presentation (fever and hypotension) to avoid missing this diagnosis since the only confirmatory test is sampling a known effusion.

The presentation is always acute, with hectic fevers and frank rigors. Tachycardia is invariably present; other findings vary, based on the underlying etiology. An evanescent three-component pericardial rub (early diastole, late diastole, and systole) is found in about one-third of cases. Tamponade can develop rapidly, as an effusion of 500 cm³ can accumulate rapidly over several days. It is important to note that, after cardiac surgery, the pericardium is not typically closed; thus, a suppurative infection will not result in tamponade, making the diagnosis even more difficult in these patients.^{12,13}

Previously, the most likely manner in which a patient developed suppurative pericarditis was through pneumonia with empyema development; the most common organism was *Streptococcus pneumoniae*. The accepted etiologies of suppurative pericarditis include seeding from circulating bacteremia, contiguous intrathoracic source (empyema), penetrating trauma, surgical wounds (sternal osteomyelitis), intracardiac source, esophageal rupture with fistula formation, retropharyngeal abscess, and hepatic/subdiaphragmatic abscess. One study by Rubin demonstrated the risk of infectious endocarditis (IE) leading to pericardial disease; at autopsy, 13% of patients with IE had suppurative pericarditis, and 20% had a myocardial abscess (this figure increased to 36% if the microbe was *Staphylococcus aureus*).^{12,15}

The current microbiology of pericardial infections has changed with the advent of antibiotics, as well as with the development of thoracic and cardiac surgery. Several recent studies note the trend toward more diverse microbes involved and an important finding of anaerobes as a common cause. Since anaerobes are the leading flora of the oral cavity, where they outnumber aerobes 100 to 1, it follows

that they would be the infectious agents if the source were esophageal, pharyngeal, GI, or pulmonic (aspiration). One large retrospective study by Brook and Frazier found primary anaerobic infections in 40% of bacterial pericarditis cases and mixed (aerobic/anaerobic) in 13%, but there were no clinical or diagnostic differences found between these types of infections.^{15,16}

Optimum therapy should include 4 weeks of a bactericidal drug, with the microbe's sensitivity known. Antibiotics penetrate well into the pericardial sac so that intrapericardial instillation is not necessary. Surgical pericardial drainage is also recommended, not only to eradicate gross pus but also to prevent constriction from occurring (a late complication with a variable time course). There has been recent evidence that supports the use of video-assisted thoracoscopic surgery (VATS) in place of open thoracotomy.¹⁷ If the patient were unable to tolerate these procedures, intrapericardial catheter placement would be advised. This is an old therapy that has had resurgence with multiple recent studies demonstrating its effectiveness and safety. Streptokinase and streptodornase can be instilled and the catheter clamped, then flushed out and the procedure repeated. These substances aid in the drainage of clotted blood and thickened nucleoproteins (pus) and significantly improve resolution of loculated effusions. This procedure does not affect systemic coagulation studies and has no increased bleeding events associated, but does prevent development of constrictive disease.^{18,19}

FUNGAL

Although there are many fungi known to cause purulent pericarditis, *Histoplasmosis* and *Candida* are the most common. These organisms usually affect immunosuppressed patients (leukemia, organ transplant, AIDS, long hospital stay on multiple antibiotics), but there are differences between these two organisms.

Histoplasmosis capsulatum spores are found in the soil of the Ohio and Mississippi river valleys, and are inhaled, causing a pneumonitis. From there, hematogenous spread occurs to the mediastinal nodes and reticuloendothelial system until cellular immunity develops. In immunocompetent individuals, this process takes about 10 to 14 days and has a self-limited course. But in an immunosuppressed individual, pericardial disease can occur from the primary infection or at a later time from reactivation; in the latter case, the source is usually adjacent mediastinal nodes, although rarely it is disseminated disease. Ten percent of patients clinically infected will develop pericardial disease.^{3,4,20}

Candida albicans and *C. tropicalis* are common host flora that can infect even immunocompetent individuals under certain circumstances. Intravenous drug abuse, indwelling venous catheters (particularly for parenteral nutrition with lipids), thoracic surgery, and prosthetic heart valves are risk factors for pericarditis from these entities. The route is typically hematogenous, intracardiac, or contiguous spread from a surgical site. The presentation for fungal infections is similar to bacterial, but the course is slightly slower in terms of effusion accumulation and pericardial thickening and scarring.

Therapy is similar to that of bacterial pericarditis, with systemic antifungal therapy and open drainage/pericardial resection.^{3,4,21}

TUBERCULOUS

Still the leading cause of chronic pericardial disease and constriction worldwide, tuberculosis (TB) incidence in the United States fell by 5% per year until 1985 and the increased spread of HIV. TB is now estimated to be the cause of 2% to 4% of all admitted pericarditis patients and 5% to 6% of cases with pericardial constriction. The reported incidence of pericardial involvement among patients with pulmonary tuberculosis ranges from 1% to 8%; evidence of active pulmonary disease at the time is rare, however, with only 11% to 50% of patients with pericarditis having positive sputum cultures.^{15,22} Pericardial involvement can occur with a primary infection or reactivation of latent infection. The most common pathway is retrograde extension via lymphatics from peribronchial and mediastinal nodes; other recognized pathways include hematogenous spread from distant foci (genitourinary or skeletal) and direct extension from a contiguous source (lymph nodes, lung, pleura, spine).

Four pathologic stages have been identified: (1) *fibrinous*—fibrin deposition with many polymorphonuclear neutrophils (PMNs), abundant organisms, and loose granuloma formation; (2) *effusive*—serosanguineous effusion accumulation with lymphocytes and monocytes predominating; (3) *absorptive*—effusion diminishes, mycobacterium cells are now scarce, and dense caseating granulomas thicken the pericardium; and (4) *constrictive*—granulomas replaced by fibrous tissue that begins to contract. Calcification may occur at any pathologic stage.^{3,22,23}

Unlike patient with bacterial pericarditis, these patients have a subacute/chronic course. The onset is insidious, with nonspecific features only, until late in the course. Diagnosis can be made by stain or culture of pericardial fluid, although this is positive in only 15% of patients clinically diagnosed with tubercular disease. These figures can be improved by doing an enzyme-linked immunosorbent assay (ELISA) and polymerase chain reaction (PCR) assay on the fluid. Pericardial biopsy is thought to have the highest diagnostic yield, although still not 100%, and is dependent on the stage of disease and amount of tissue obtained. Purified protein derivative (PPD) testing is not helpful since patients may be anergic (low sensitivity), or may be reactive but have no pericardial involvement (low specificity). Treatment consists of four-drug therapy for at least 1 month, followed by two-drug therapy for 1 to 2 years. Careful follow-up is needed to evaluate for signs of constriction, and some recommend pericardiectomy as initial therapy due to the high percentage (30%–50%) of appropriately treated patients that still develop constriction by 4 months. Steroids should also be given in the first month; they have been shown to significantly decrease mortality and improve patient symptoms, although they have little effect on pericardial constriction.^{2,22,23}

HIV INFECTION

Significant cardiac morbidity due to HIV disease is estimated at 6% to 7%, with pericardial effusion and myocarditis the most common abnormalities. At autopsy, 40% of patients have large

effusions, and several studies have found that an effusion is an independent risk factor (separate from CD4 count) for decreased survival. In a study of HIV patients, 25% had an effusion by echocardiography, of which 20% were large. The majority were asymptomatic; at follow-up, 42% of the effusions had spontaneously resolved. Still, in a series of patients requiring intervention for tamponade, the most common underlying disorders were malignancy and HIV.²⁴

Pericardial disease can result from opportunistic infections, medical treatment of HIV, and the HIV itself. In these immunocompromised patients, one must consider not only viral and bacterial pathogens but also fungal, mycobacterial, and parasitic infections,^{25,26} as well as noninfectious causes such as lymphoma and Kaposi's sarcoma. The risk factors for death associated with moderate–severe pericardial effusion are tuberculosis (OR 47.2), heart failure (OR 30.3), other pulmonary infection (OR 15.0), and Kaposi's sarcoma (OR 8.6). Based on this information, it would be prudent for an HIV patient symptomatic with a persistent pericardial effusion to be empirically treated for tuberculosis until that diagnosis can be excluded.²⁵

RENAL FAILURE

Uremic pericarditis occurs in 6% to 10% of patients with advanced renal disease before or shortly after starting dialysis and correlates with the degree of azotemia; it is unusual to occur with a BUN < 60 mg/dL. Treatment is initiation or intensification of dialysis with avoidance of heparin because of concern for a hemorrhagic effusion. Dialysis-associated pericarditis occurs in 13% of patients receiving hemodialysis and, occasionally, peritoneal dialysis; the etiology and treatment are unclear.^{3,6}

MYOCARDIAL INFARCTION

Pericarditis can occur early in the first few days post–myocardial infarction (MI) due to transmural infarction that causes inflammation of the local pericardium. It is a marker of larger infarct size, but it is not associated with increased morbidity or mortality. The incidence has decreased significantly since reperfusion therapies have become the standard of care for MI.²⁵ Treatment is full-dose aspirin while avoiding other nonsteroidal anti-inflammatory drugs (NSAIDs) or steroids that prevent scar formation and may increase the incidence of myocardial rupture. Delayed pericarditis, also known as Dressler's syndrome, is due to a diffuse immunopathologic process involving the entire pericardium and is the same etiology of postpericardiotomy syndrome. It is best treated with ibuprofen or colchicine.^{5,27,28} Corticosteroids are best avoided post-MI due to increased risk of myocardial rupture, and are associated with increased risk of relapsing pericarditis. Colchicine should be used with caution or avoided in patients with renal or hepatic insufficiency, blood dyscrasias, or GI motility disorders due to increased risk of severe toxicity.⁸

Discerning pericarditis from acute MI can be challenging since the clinical presentation of chest pain, EKG abnormalities and even elevated serum troponin levels can be similar. These patients are often taken for emergent angiography to rule out an acute coronary occlusion, but may have complications

from the antithrombotic (heparin) and antiplatelet (aspirin, clopidogrel) agents causing hemorrhagic pericardial tamponade. Bedside echocardiography may be able to identify normal left ventricular contractility versus regional abnormalities that correlate to EKG leads and coronary distribution.²⁹

AUTO REACTIVE

Pericarditis is associated with numerous autoimmune and collagen-vascular diseases. It is necessary to first evaluate for uremic, infectious, or neoplastic causes. Once these are ruled out, intensifying treatment of the underlying conditions and symptomatic analgesics are helpful. Intrapericardial steroids offer extended effectiveness without the systemic adverse effects.^{30,31}

NEOPLASTIC

Mesothelioma is the most common primary pericardial malignancy, but metastatic cancers (lung, breast, lymphoma, melanoma) are 40 times more likely to cause pericardial disease. Twenty percent of large effusions without an obvious cause have been found to be due to an undiagnosed malignancy. Neoplastic effusions are typically exudative, fibrinous, and hemorrhagic, and often require open surgical drainage. Intrapericardial chemotherapy and sclerosing agents are an option if tamponade does not exist.^{3,32}

Traumatic

Hemopericardium may occur secondary to penetrating or blunt chest trauma; pericardial rupture may occur following blunt injuries causing cardiac herniation that presents as tamponade. From 17% to 45% of type A aortic dissections are complicated by hemopericardium. In these cases, unless the patient is in extremis due to tamponade, pericardiocentesis is contraindicated due to potentially extending the dissection.³³ Invasive procedures, such as endomyocardial biopsy, electrophysiology (EP) studies, permanent pacemaker insertion, and coronary angiography, can cause unintended cardiac or vascular perforation, producing tamponade. EP procedures have a 1% to 6% risk of cardiac perforation, with the risk increased by higher energy use and ablations for atrial fibrillation. Coronary perforation occurs in 0.1% to 0.6% of all percutaneous coronary interventions (PCIs), resulting in 42% mortality; its risk is increased by atheroablative procedures. The immediate treatment is to seal the coronary injury and reverse all anticoagulation while monitoring closely for tamponade.^{4,8,33}

TAMPONADE

Pericardial tamponade is due to pericardial pressure exceeding cardiac chamber diastolic pressure, therefore not allowing filling to occur. While there are several risk factors for developing pericardial tamponade (Table 22-3), only three factors determine the clinical presentation: (1) volume of fluid; (2) rate at which fluid accumulates; and (3) pericardial compliance. The pressure–volume curve is nonlinear, with the initial flat section due to the pericardial reserve volume. This volume is made up of the recesses and sinuses of the pericardial sac



TABLE 22-3: Common Risk Factors for Pericardial Tamponade

History of pericarditis
Blunt or penetrating chest trauma
Cardiac surgery
Cardiac catheterization (PCI or EP study)
Known or suspected intrathoracic neoplasm
Known or suspected aortic dissection
Renal failure or hemodialysis

(Figure 22-2). The gradual upslope of the curve is due to the elastic fibers stretching and the wavy collagen fibers straightening. The steep slope is due to the exhaustion of these mechanisms; any increase in volume above that critical point causes severe increases in pressure that are transduced as compressive forces on the heart. If the fluid accumulates rapidly or if the pericardium is pathologically stiff, then relatively small amounts of fluid can result in marked elevations in pressure. In contrast, if the effusion grows slowly, the pericardium can gradually stretch to accommodate the volume, stretching the pressure–volume curve to the right.^{2,4,34} It should be noted that approximately a third of patients with large idiopathic effusions develop tamponade unexpectedly.³⁵

Symptoms of tamponade include dyspnea, tachypnea, and fatigue, while signs include tachycardia, elevated jugular venous distension, a quiet precordium, hypotension, and pulsus paradoxus. Another notable finding is dullness to percussion at the left scapular angle with bronchial breath sounds due to

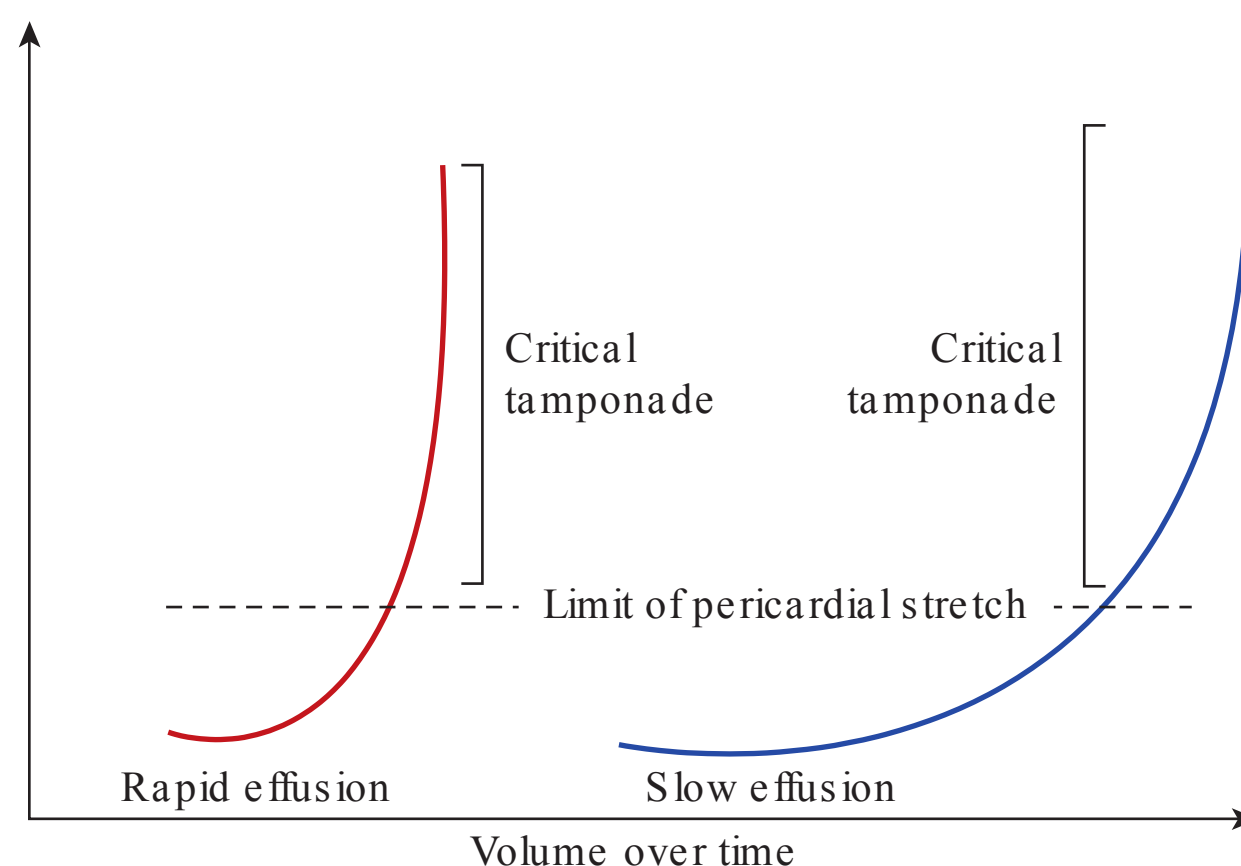


FIGURE 22-2 Cardiac tamponade. Pericardial pressure–volume (or strain–stress) curves are shown in which the volume increases slowly or rapidly over time. In the left-hand panel, rapidly increasing pericardial fluid first reaches the limit of the pericardial reserve volume (the initial flat segment), quickly exceeds the limit of parietal pericardial stretch, causing a steep rise in pressure, which becomes even steeper as smaller increments in fluid cause a disproportionate increase in the pericardial pressure. In the right-hand panel, a slower rate of pericardial filling takes longer to exceed the limit of pericardial stretch, because there is more time for the pericardium to stretch and for compensatory mechanisms to become activated. (Reproduced with permission from Spodick DH: Acute cardiac tamponade, *N Engl J Med* 2003 Aug 14;349(7):684–690.)

compressive atelectasis from the effusion. It is often commented that a pericardial rub disappears when an effusion develops, but a rub may still be present (typically on inspiration) caused by pericardial–pleural friction. The elevated pericardial pressure results in elevated right atrial and venous pressure giving a characteristic jugular venous waveform lacking the Y descent. These changes result from decreased right atrial emptying due to impaired ventricular expansion and filling.^{4,34,36}

The description of *pulsus paradoxus* by Kussmaul in 1873 was of the “paradox” of not palpating a pulse despite detecting a heartbeat during inspiration. It has since been described in patients with normal physiology that during inspiration there is a consistent decrease in left ventricular stroke volume (7%) and arterial pressure (3%). These effects are due to ventricular interdependence and can be accentuated in pericardial disease, leading to the suggested renaming of the finding as *pulsus exageratus* (Figure 22-3). It is thought to be pathognomonic of tamponade when positive (inspiratory drop in systolic blood pressure [SBP] of 10% or 10 mm Hg), but there can be false positives as well as false negatives. A pulsus exageratus may be present without tamponade in severe chronic obstructive pulmonary disease (COPD)/asthma or with a large pulmonary embolism; exaggeration of intrathoracic pressures is believed to be responsible. Tamponade may be present without a pulsus in hypovolemia, called low-pressure tamponade; if blood

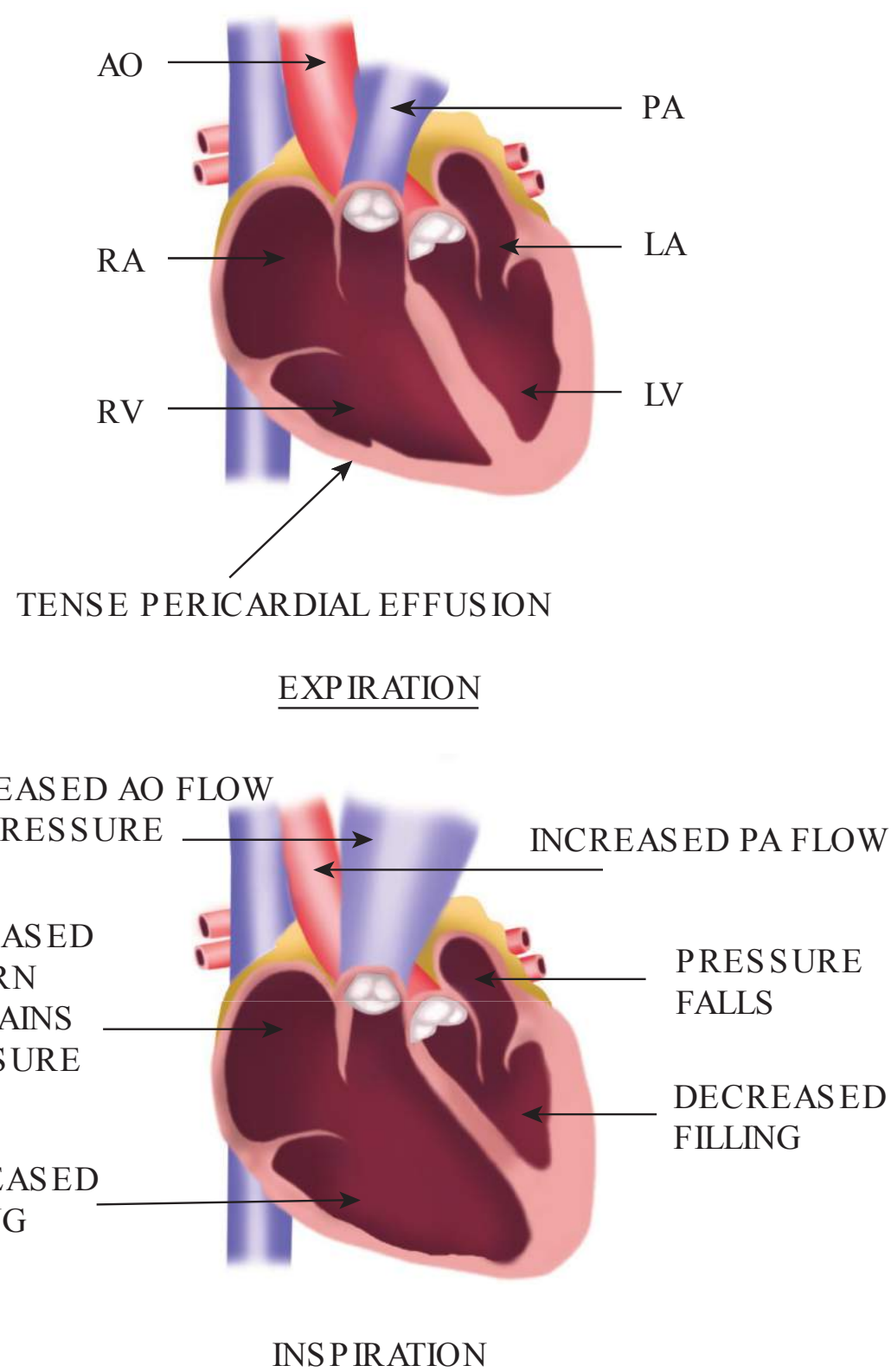


FIGURE 22-3 Schematic representation of the competitive ventricular filling that occurs during respiration with pericardial tamponade. (Reproduced with permission from Cosio FG, Martínez JP, Serrano CM, et al.: Abnormal septal motion in cardiac tamponade with pulsus paradoxus, *Chest* Jun;71(6):787–788, 1977.)

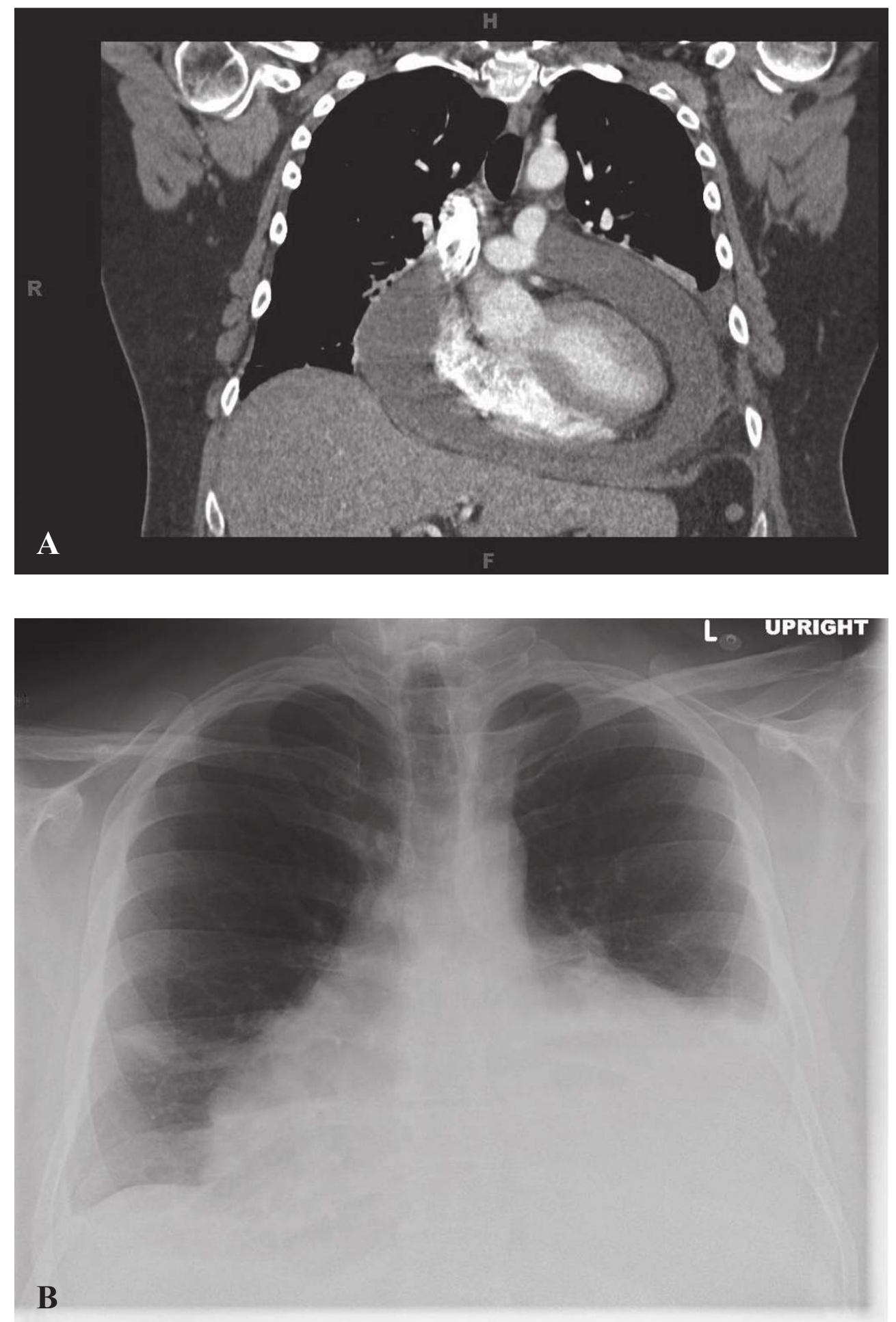


FIGURE 22-4 Chest radiograph (A) and CT (B) of an asymptomatic patient with a large idiopathic effusion.

volume/preload is already diminished, minimal increases in pericardial pressure limit right-sided filling without causing an effect on left-sided function. Alternatively, an atrial septal defect will shunt blood from left to right, nullifying ventricular interdependence. Finally, right ventricular hypertrophy causing a thick, noncompliant septum, aortic regurgitation, congestive heart failure (CHF), and severe left ventricular hypertrophy all increase left ventricular end-diastolic pressure (LVEDP); these conditions also limit ventricular interdependence and therefore limit the formation of a pulsus.^{4,34,36}

There are several diagnostic tests that can assist in the diagnosis of tamponade; a chest radiograph is not one of them since it gives only static anatomic data, not dynamic functional data. Acutely, the pericardial silhouette will be normal, requiring approximately 250 cm³ of fluid to gather before it assumes a globular shape (Figure 22-4). But even if this finding is present, it still does not prove that the effusion is causing any pathologic effects. Likewise, there are EKG findings suggestive of pericarditis (diffuse ST abnormalities; Figure 22-5) or an effusion (low voltages due to insulating effects, and electrical alternans; Figure 22-6), but these also are not helpful in diagnosing tamponade.^{5,8,33}

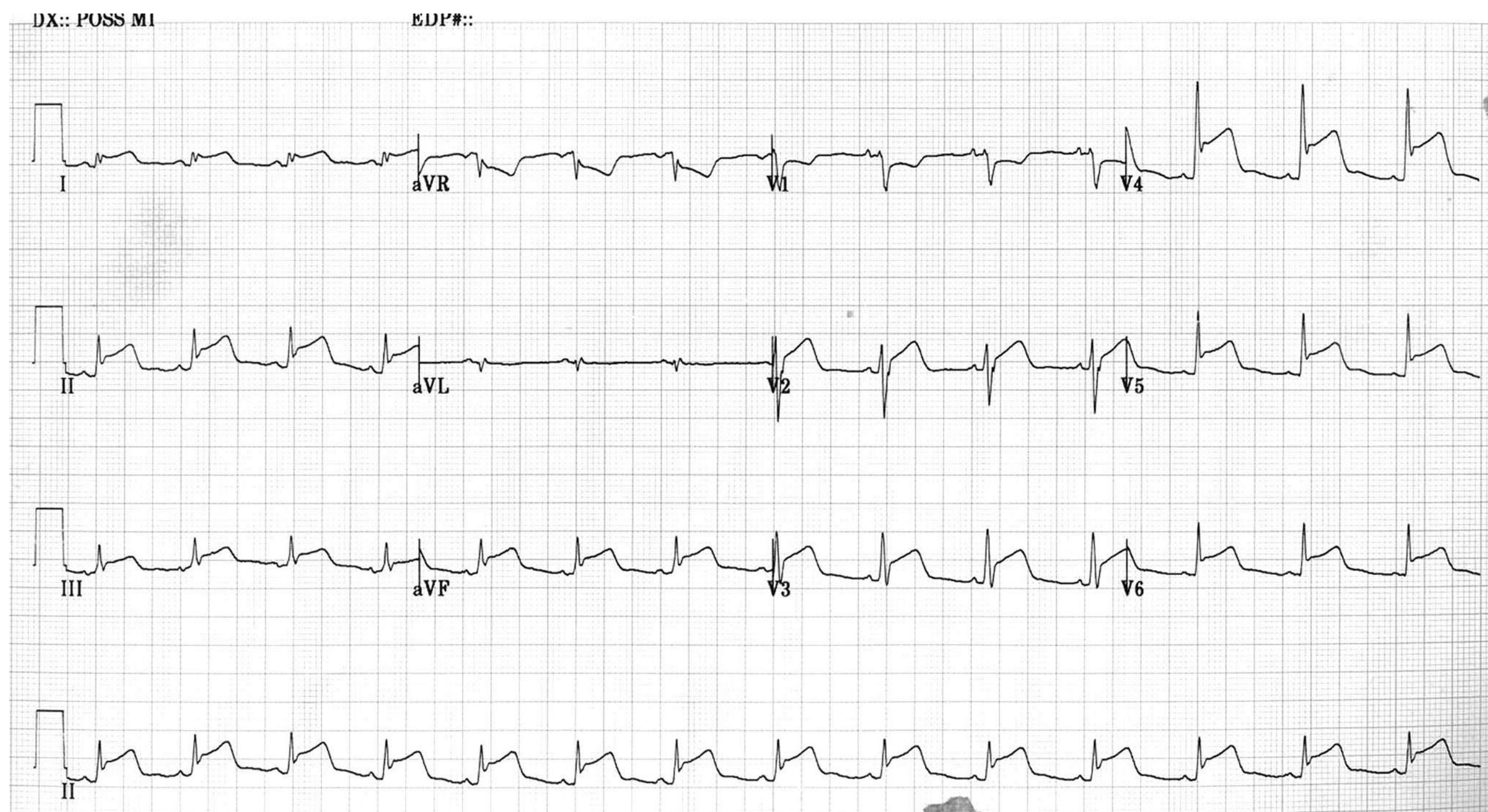


FIGURE 22-5 An EKG of an adolescent with fever and chest pain during an episode of diabetic ketoacidosis. Note ST-segment elevations in all leads except aVL (an isoelectric lead here, thus the ST segment is compressed) and aVR and V1, which have expected ST-segment depressions. PR-segment depression is best seen in lead II.

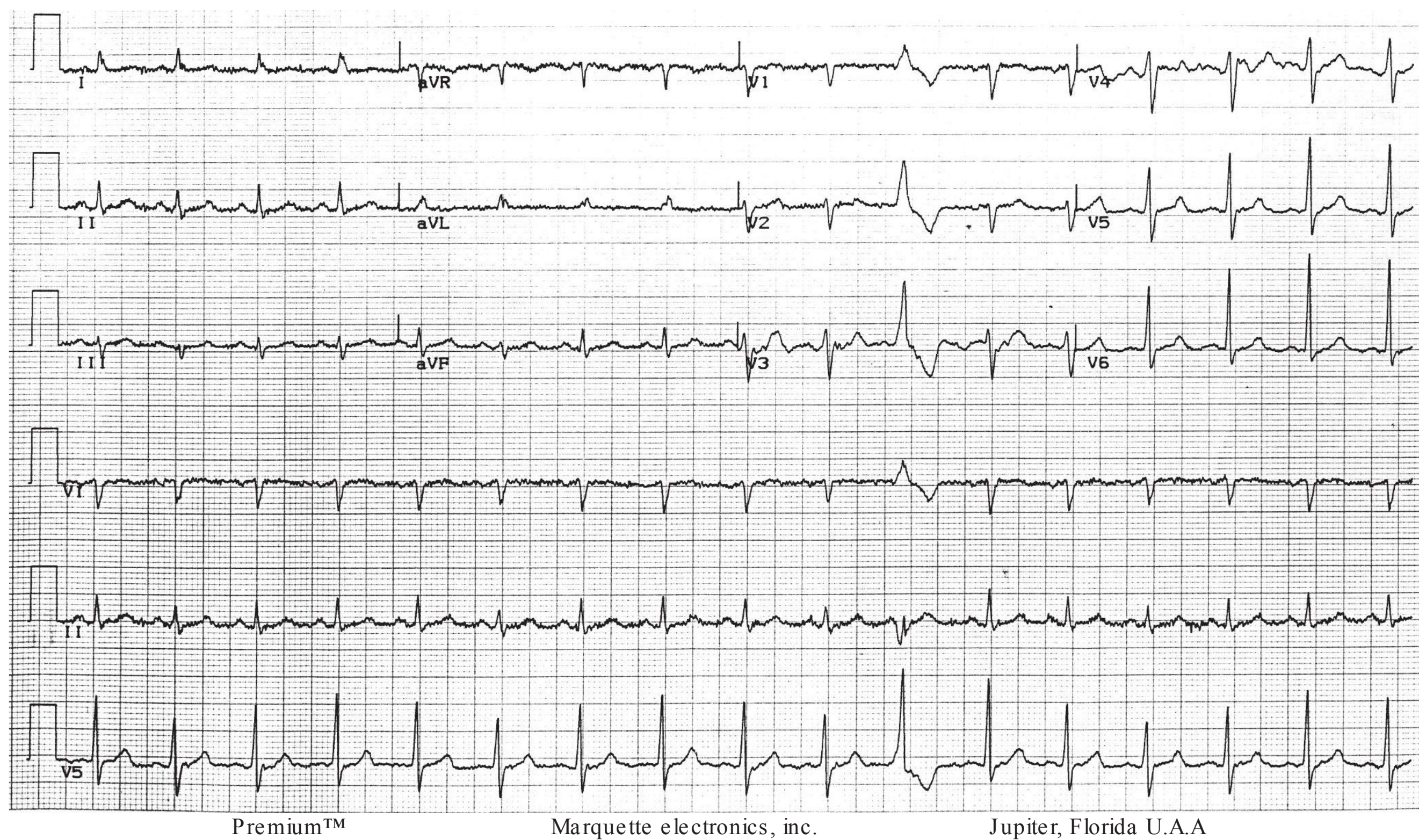


FIGURE 22-6 EKG of a patient with end-stage renal disease on chronic hemodialysis with a large, symptomatic effusion. Electrical alternans is present, with the voltages varying over a three-beat cycle. Mild tachycardia (rate 102) and low voltages in the limb leads are also present. A pericardial window was performed.

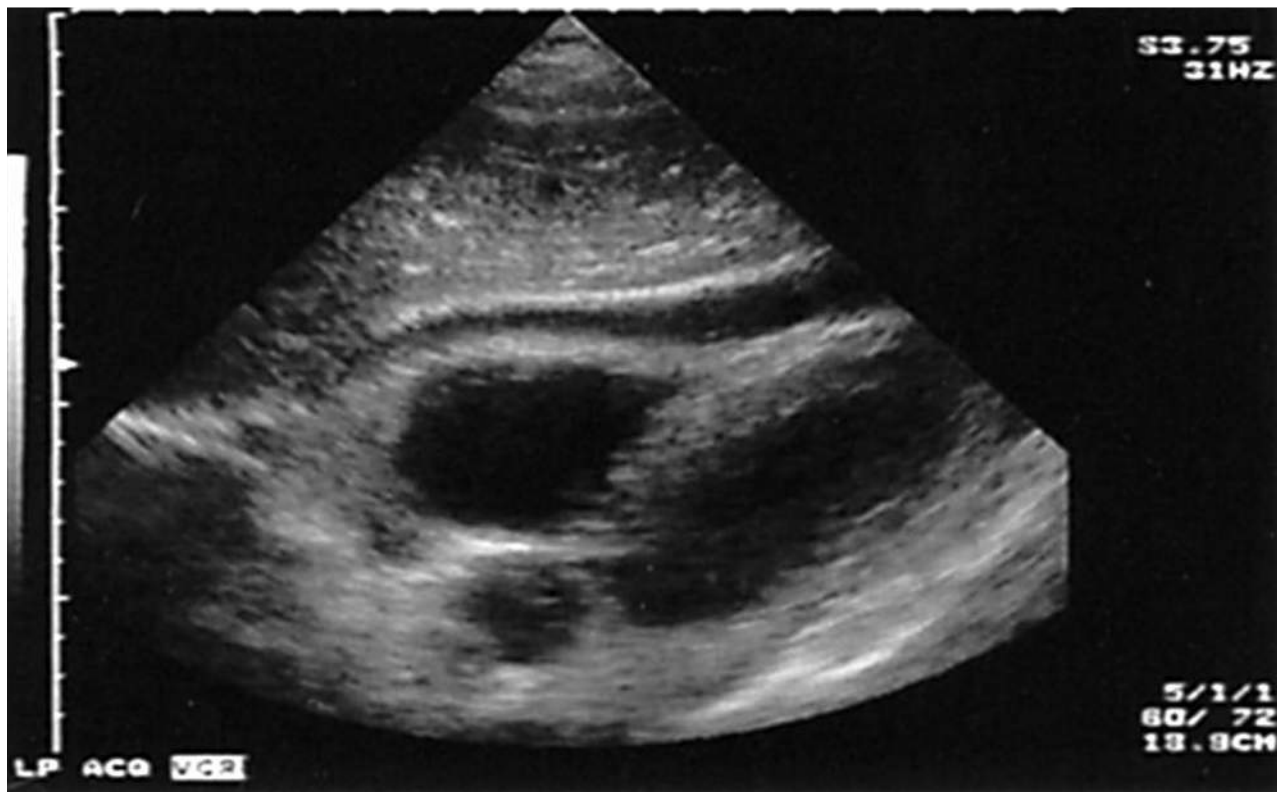


FIGURE 22-7 Subxiphoid pericardial ultrasound reveals a large pericardial fluid collection. (Reproduced with permission from Brunicaudi FC, Andersen DK, Billiar TR, et al: *Schwartz's Principles of Surgery*, 10th edition. New York: McGraw-Hill Inc; 2014.)

Echocardiography is a valuable noninvasive means to evaluate a patient for tamponade, but it should be remembered that no single finding has 100% sensitivity or specificity. The presence of an effusion, graded as small (posterior only), moderate (anterior also but < 1 cm), or large (> 1 cm) is required, but alone does not confirm tamponade (Figure 22-7). Right atrial collapse is more sensitive, but less specific, for tamponade than right ventricular diastolic collapse. Collapse occurs first where chamber pressures are lowest, so that left atrial and then ventricular collapse normally occur late unless right-sided chamber pressures are elevated due to pulmonary hypertension. In that case, left atrial collapse may precede right atrial and ventricular collapse⁶ (Figure 22-8). The absence of inferior vena cava (IVC) plethora (suggesting normal right atrial pressure) makes the diagnosis of tamponade unlikely.

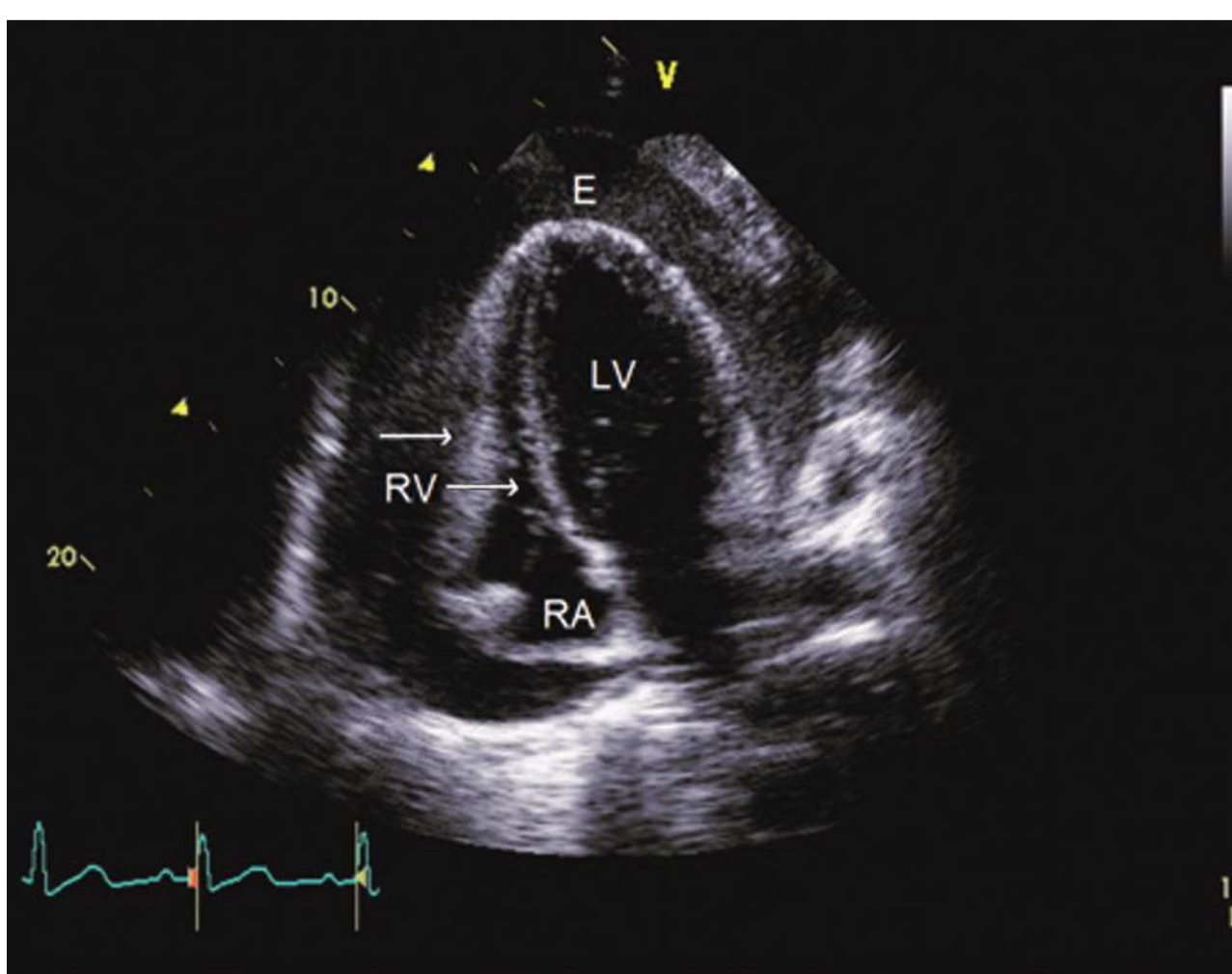


FIGURE 22-8 RV compression (arrow) in cardiac tamponade (apical four-chamber plane). RA, right atrium; RV, right ventricle; LV, left ventricle; E, effusion. (Reproduced with permission from Fuster V, Walsh RA, Harrington RA: *Hurst's the Heart*, 13th edition. New York: McGraw-Hill Inc; 2011.)

Flow velocity paradoxus, the immediate marked decrease in transmitral (and increase in transtricuspid) Doppler flow with inspiration, like the pulsus, is an accentuation of normal physiology.^{37,38}

On right-heart catheterization, pulmonary artery wedge pressure and atrial and ventricular end-diastolic pressures are elevated and equalized (within 5 mm Hg) in tamponade. These values reflect the elevated intrapericardial pressure, but again there are other pathologic conditions that can cause diastolic equalization of pressure.

For hemodynamically stable patients (including those patients stabilized with the use of fluids and vasopressors), a controlled drainage of the effusion under guided imaging is preferable. This procedure can be done bedside with echocardiography or in the cardiac catheterization lab under fluoroscopy while monitoring right- and left-heart pressures. A catheter is usually left in the pericardium for at least 72 hours to continue draining any recurrent effusion. Surgical drainage employing either a subxiphoid pericardial window or an open thoracotomy is also an option.

For hemodynamically unstable patients, immediate relief of the tamponade by percutaneous subxiphoid needle aspiration is required (Figure 22-9). The patient should be positioned upright at 45° in order to have gravity assist the fluid into a dependent position anteriorly. If ultrasonography is not available, a precordial lead can be clipped to the metal hub of the needle, and a continuous EKG strip is run while aspirating. Epicardial contact is indicated by ST-segment elevation

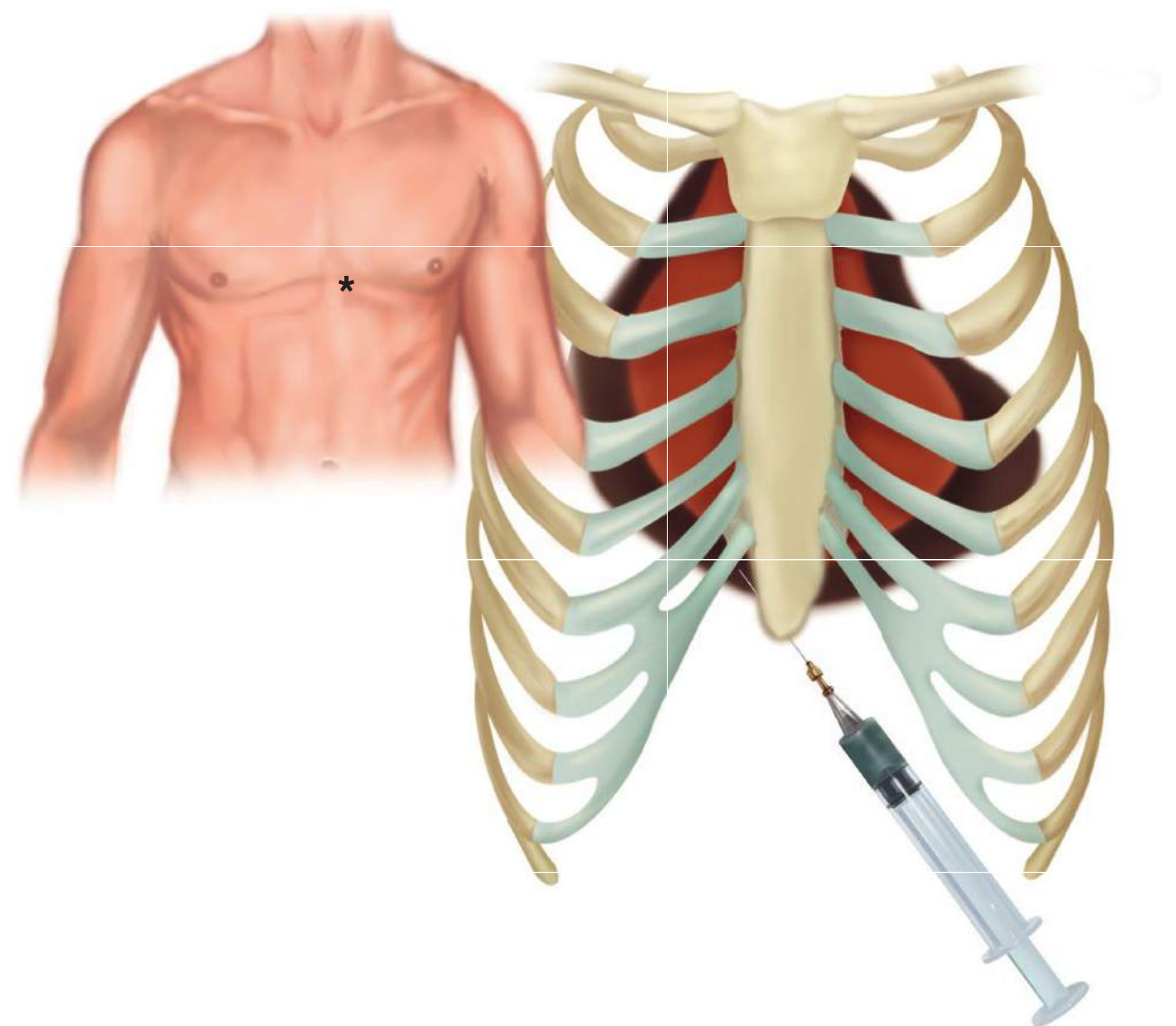


FIGURE 22-9 The paraxiphoid technique for *pericardiocentesis* is usually performed with the needle directed toward the left shoulder or left scapula tip. However, if one aims toward the tip of the right scapula, the needle tends to go parallel to the lateral border of the right heart and is less apt to penetrate the coronary artery or myocardium. (Reproduced with permission from Henning RS: *Critical Care Cardiology*. New York: Churchill Livingstone; 1989.)

or premature ventricular contractions (PVCs) indicating that the needle should be withdrawn slightly. Potential serious complications include ventricular puncture, coronary artery laceration, and pneumothorax.^{33,39} Medical therapy alone is not adequate for acute tamponade, but a volume challenge can be given while preparing for pericardial drainage. Vasoactive infusions are not typically helpful since cardiac inotropy and chronotropy are usually maximal already, and simply increasing vascular tone decreases tissue perfusion. Positive pressure ventilation should be avoided if possible since it will further reduce cardiac filling and exacerbate the tamponade effects.^{40,41}

Constriction

Constriction has been referred to as pseudocirrhosis because of its ability to mimic chronic liver disease. The most common etiologies include postradiation, lung and breast cancer, TB, and renal failure. The final common pathway is thickening and scarring of the pericardial layers, which, in turn, become adherent, obliterating the pericardial space. There can be focal disease, usually involving the apex and the right atrium (particularly the atrial–ventricular groove), due to increased local friction, and a minority of cases can have constriction resulting from the visceral pericardium alone.^{1,3} Whatever the cause or location, the fibrotic encasement causes a fixed diastolic chamber volume with impaired expansion and an isolation of the cardiac chambers from changes in intrathoracic pressure.

Normally, the majority of ventricular filling occurs in phase 2 (rapid filling) of diastole, with up to 20% during phase 4 (atrial contraction), and increasing heart rate shortens diastole, decreasing filling. With constriction, elevated atrial pressures cause increased ventricular filling (75%) in the first phase of diastole, which is then halted abruptly by mid-diastole. In this case, increasing heart rate actually improves cardiac output since very little filling occurs in the shortened late diastole.

With the abrupt cessation of filling, a “knock” is produced in 30% to 70% of patients; it is a loud diastolic sound 0.6 to 0.12 seconds after S2, but of higher frequency than an S3. Respiratory pressure variations are still transmitted to other intrathoracic structures (vena cava, pulmonary vasculature) but not to the heart. Inspiration reduces the pressure gradient between the pulmonary veins and the left heart, resulting in decreased diastolic flow and ventricular filling; based on accentuated ventricular interdependence, the septum shifts leftward, allowing a simultaneous increase in right ventricular filling. The opposite effects are seen with expiration. In pure constrictive pericarditis (CP), the pulsus is usually less than 10 mm Hg and, if greater, suggests concomitant tamponade (effusive–constrictive pericarditis).^{1,3,42}

The onset of constrictive disease is typically insidious, with symptoms developing from weeks to decades after the inciting event. In one study by Ling, the average duration of symptoms prior to a diagnosis was 23.4 months.⁴³ Peripheral edema, abdominal swelling (from hepatomegaly or ascites),

dyspnea, and orthopnea are common initial complaints, illustrating the potential confusion with intrinsic liver disease. Physical exam will reveal elevated jugular venous pressure (JVP) in 96% of patients, and Kussmaul’s sign (paradoxical increase in JVP with inspiration, since the right atrium cannot accommodate the increased venous return) may be present. It is not specific for constriction, however, and may be seen in any condition with elevated right heart pressures, including right ventricular infarct, pulmonary hypertension, tricuspid stenosis, and restrictive cardiomyopathy (RCM). Early cessation of diastolic filling produces Fridreich’s sign, a rapid *Y* descent of the JVP, seen in 94% of cases in one series. A dampened apical impulse and a pericardial knock, more prominent with squatting but attenuated by nitroglycerin, are also common findings. Pulsatile hepatomegaly with ascites was found in 70% of patients in one study, but there are differences in the liver function tests and ascitic fluid analysis of these patients with passive congestion compared with those of cirrhotic patients, as seen in a study by Runyon.^{42,44}

EKG findings include low voltages (60%) and atrial fibrillation in the late stages (25%), although these are insensitive and nonspecific. Diagnosis can be made by CT or MRI, demonstrating a pericardial thickness of greater than 4 mm, sometimes with calcifications. However, since there may be focal disease only, relying on these modalities will miss a certain percentage of cases. Echocardiography can be useful in evaluating for constriction, with transesophageal being superior to transthoracic echo in detecting pericardial thickening. Other echo findings include preserved systolic function, with rapid diastolic filling causing exaggerated posterior wall and septal motion (septal bounce), early closure of the mitral valve, and premature opening of the tricuspid valve.

RCM, such as that caused by amyloidosis, sarcoidosis, hemochromatosis, glycogen storage diseases, or endomyocardial elastosis, may have a similar clinical presentation and echo abnormalities to constrictive pericarditis. It is still a challenge for cardiologists to differentiate the entities (short of sending a patient for a thoracotomy). There have been studies that have found a faster filling rate with a shorter interval to peak filling in constriction, and Garcia et al. used Doppler tissue imaging to show that left ventricular expansion peak velocity is markedly reduced in restrictive disease, but is preserved in constriction.⁴⁵

Cardiac catheterization can also be used to help make the diagnosis, but again there is overlap of many of the findings with RCM. Right atrial pressure tracings show the typical *M* or *W* pattern formed by the prominent *Y* descent. Diastolic pressures are elevated and approximately equal in all four chambers, with simultaneous ventricular tracings giving a characteristic dip and plateau pattern (square root sign); right ventricular end-diastolic pressure (RVEDP) has been found to be at least one-third of right ventricular systolic pressure (RVSP) in 95% of constriction. If all chamber diastolic pressures are low, and there is clinical suspicion of CP, a rapid infusion of 1 L of saline may be given to identify occult disease; in a normal patient, the pressures should rise and separate, but with CP they rise and remain equally related.^{4,43}

Medical therapy using diuretics may be initially attempted, but the overwhelming majority of patients will require pericardiectomy as definitive therapy. In a large series from the Mayo Clinic, preoperative risk factors were identified as severity of RVEDP elevation, renal insufficiency, and previous mediastinal radiation; intraoperative risk factors that worsen prognosis were unresectable calcifications and incomplete decortication (usually due to involvement of the epicardium). Poor postoperative response is found when the fibrosis and calcification had progressed to involve the myocardium as well. Operative mortality is based on New York Heart Association (NYHA) functional class status, with 1% for class I or II, 10% for class III, and 46% for class IV; these data illustrate the importance of making the diagnosis sooner rather than later.^{42,43}

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GASTROINTESTINAL AND RENAL DISORDERS

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Gastrointestinal Bleeding

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Taylor M. Zeglam

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INTRODUCTION

Gastrointestinal (GI) bleeding is an important cause of mortality for emergency department (ED) and critically ill patients. Upper gastrointestinal bleeding (UGIB) is defined as a gastrointestinal bleeding source proximal to the ligament of Treitz, whereas lower gastrointestinal bleeding (LGIB) is defined as bleeding distal to the ligament of Treitz (Figure 23-1). This chapter discusses the epidemiology, clinical presentation, and etiology of UGIB and LGIB, followed by a discussion of the management of patients with GI bleeding.

UPPER GASTROINTESTINAL BLEEDING

Epidemiology

In the United States, UGIB occurs in 50 to 150 cases per 100,000 adults per year, and accounts for 400,000 hospital admissions and 30,000 deaths annually.¹⁻³ With a mortality rate ranging from 3% to 16%, UGIB is an important cause of mortality in the ED.⁴⁻¹¹

Hospital inpatients presenting with UGIB have a 2- to 6-fold increase in mortality compared with their ED counterparts.⁴⁻¹¹ Increased risk of mortality is associated with increased age, severe comorbidity, hypotension, shock, rebleeding, and the timing of the bleeding event during an inpatient hospital stay.^{5,12}

Although the overall incidence of nonvariceal UGIB has declined in recent years, an increasing proportion of elderly individuals present with acute UGIB; up to 70% of acute UGIB occurs in patients greater than 60 years of age.^{2,13}

Clinical Presentation

Patients with UGIB often present with hematemesis, coffee ground emesis, melena, maroon stool, or hematochezia. Blood that accumulates rapidly in the stomach may be vomited as bright red blood (i.e., hematemesis). Slower bleeding or brisk bleeding that becomes stagnant due to obstruction may become partially digested, resulting in “coffee-ground” appearance. Melena, or dark black, tarry stools, is usually suggestive of a UGIB, but can also be due to more distal bleeding, as far distal as the cecum. Hematochezia, the passage of fresh, bright red blood through the rectum, represents rapid bleeding, usually from a lower GI source, but sometimes from a massive upper GI source.

The clinical presentation of GI bleeding depends on the amount and location of hemorrhage. Even in the absence of overt bleeding, patients may present with complications of anemia, including fatigue, chest pain, syncope, lightheadedness, orthostatic hypotension, and shortness of breath. Untreated, manifestations of progressive hemorrhagic shock are inevitable, including acute end-organ dysfunction and refractory hypotension.

The physical exam should include an assessment of airway, vital signs, and mentation. The presentation of UGIB may be subtle, especially in the elderly. An abdominal exam, if tenderness is elicited, aids in localizing the source to a gastric or duodenal location; however, 26% of patients with peptic ulcer disease may not have pain.¹⁴ Blood on digital rectal exam may suggest both chronicity and degree of bleeding. The absence of rectal blood, however, does not exclude the existence of a GI source. Stigmata of chronic liver disease—including jaundice, telangiectasia, hemorrhoids, or caput

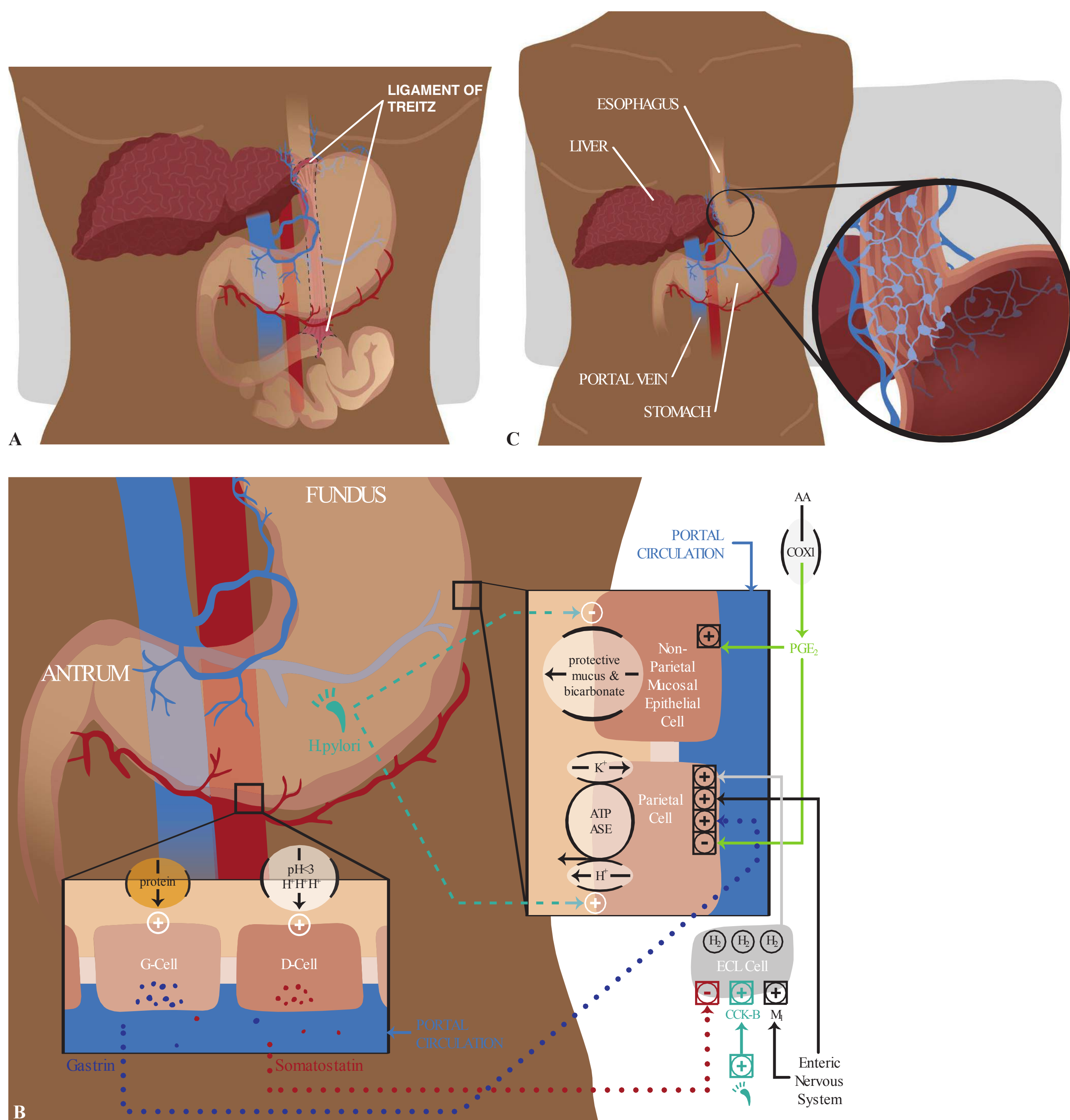


FIGURE 23-1 (A) The **ligament of Treitz** attaches the third and fourth part of the duodenum to connective tissue around the superior mesenteric artery. It demarcates the end of the upper gastrointestinal tract and the beginning of the lower gastrointestinal tract. **(B)** The gastric parietal cells generate an acidic environment via the $H^+K^+ATPase$. The mucosal epithelial cells balance the acidity and protect the gastric lining by secreting mucus and bicarbonate. Ingested protein present in the stomach stimulates G-cells to produce gastrin, which stimulates parietal cells to secrete H^+ ions. An acidic environment provides negative feedback via somatostatin from D-cells. Enterochromaffin-like (ECL) cells are located in gastric glands in the gastric mucosa and have multiple receptors, receiving positive input from the enteric nervous system (M_1) and negative input via somatostatin. When stimulated, ECL cells produce histamine (H_2) which stimulates parietal cells to secrete H^+ ions. Peptic ulcer disease (PUD) is caused by NSAIDs and *H. pylori* infection. NSAIDs inhibit the cyclooxygenase (COX) enzyme which produces prostaglandins from arachidonic acid (AA). Prostaglandins promote mucus and bicarbonate secretion from mucosal epithelial cells. NSAID use decreases the presence of these protective elements. *H. pylori* infection, again, inhibits the secretion of bicarbonate and mucus, but also activates the parietal cells and the ECL cells, causing an acidic environment, resulting in PUD. **(C)** The portal vein conducts blood from the gastrointestinal tract and spleen to the liver. Hepatic cirrhosis leads to increased hepatic resistance, resulting in portal vein hypertension and increased portal blood flow. This increase in portal pressure causes dilation of existing vessels and the formation of portocaval anastomoses, such as **esophageal varices**. These highly vascularized anastomoses are under elevated pressures and liable to bleeding in the gastrointestinal tract.



TABLE 23-1: Causes of Upper Gastrointestinal Bleeding

Peptic ulcer disease	Erosive gastritis	Esophagitis
Esophageal varices	Gastric varices	Mallory–Weiss syndrome
Stress ulcers	Arteriovenous	Malignancy
Nasal bleeding	malformation	Aortoenteric fistula
Leiomyoma	Pharyngeal	Angiodysplasia
	bleeding	
	Telangiectasia	

medusae—may indicate the presence of esophageal or gastric varices due to portal hypertension.

Etiology

UGIB can originate from a number of sources, discussed here in order of frequency. A list of causes of upper GI bleeding is listed in Table 23-1.

PEPTIC ULCER DISEASE

Peptic ulcer disease (PUD) represents a spectrum of conditions of the stomach and duodenum that result from the loss of homeostasis of the gastric milieu (Figure 23-2). The advent of H_2 -receptor antagonists, proton pump inhibitors (PPIs), and the treatment of *Helicobacter pylori* have decreased the incidence and prevalence of uncomplicated PUD. However, PUD remains the most common cause of UGIB, accounting for 140,000 hospitalizations each year in the United States.^{15–18} Approximately 22% to 59% of UGIB is caused by PUD, of which the majority is duodenal, as opposed to gastric, in origin.^{4,19,20} The annual incidence of UGIB due to PUD varies from 22 to 57 per 100,000 patients.¹⁷ GI bleeding from a duodenal location is fairly common owing to the abundant

blood supply of the duodenum and the posterior location of the gastroduodenal artery to the duodenal bulb. This is the case with most presentations of massive UGIB. The presence of large ulcers in the posterior duodenal bulb or on the lesser curvature of the stomach is associated with increased mortality.

Healthy gastric and duodenal mucosa express cyclooxygenase (COX), the rate-limiting enzyme in prostaglandin synthesis. Prostaglandins protect the mucosal lining from injury by gastric acid and pepsin. The pathogenesis of PUD results from the overproduction of gastric acid and pepsin, or from decreased mucosal protection due to COX inhibition. Overproduction of gastric acid and pepsin overwhelm the mucosal barriers and reduce mucous and bicarbonate secretion.²¹ Nonsteroidal anti-inflammatory drugs (NSAIDs) cause ulcerative disease by submucosal erosion and reduction of prostaglandin production from COX inhibition. The elevated rate of PUD witnessed in the United States parallels the high rate of NSAID use.⁴ NSAID use is currently considered the most significant risk factor associated with UGIB. Concurrent steroid use also increases the risk of ulcer formation.

Another common cause of PUD is *H. pylori*, a gram-negative bacteria residing in the mucosal layer of the stomach, which stimulates gastrin production and the release of ulcerogenic factors (e.g., platelet-activating factor and components of the complement pathway). The majority of nonbleeding duodenal (90%) and gastric (75%) ulcers are associated with *H. pylori* infections.²² Consequently, one large study found that 45% of patients with nonvariceal UGIB were positive for *H. pylori*.²³

H. pylori has been reported to be present in 58% to 78% of patients 65 years or older with PUD. The successful eradication of *H. pylori* results in ulcer healing in greater than 95% of patients.²⁴ The current consensus for first-line *H. pylori* eradication therapy consists of PPIs, clarithromycin, and amoxicillin or nitroimidazole or metronidazole for a minimum of 7 days.^{14,25} Recurrence of bleeding from *H. pylori* infection is rare when this organism is eradicated as part of ulcer treatment.^{25,26}

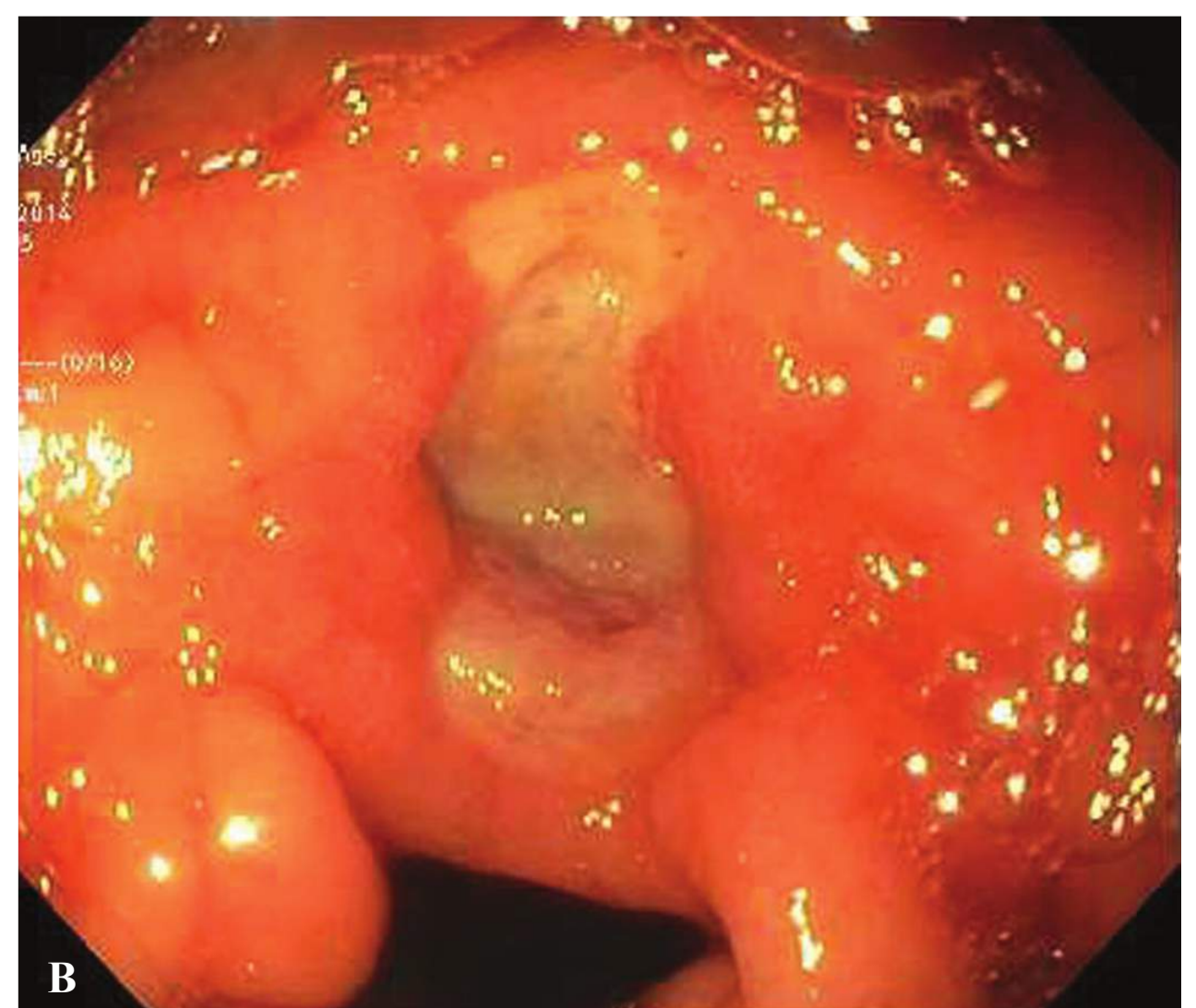
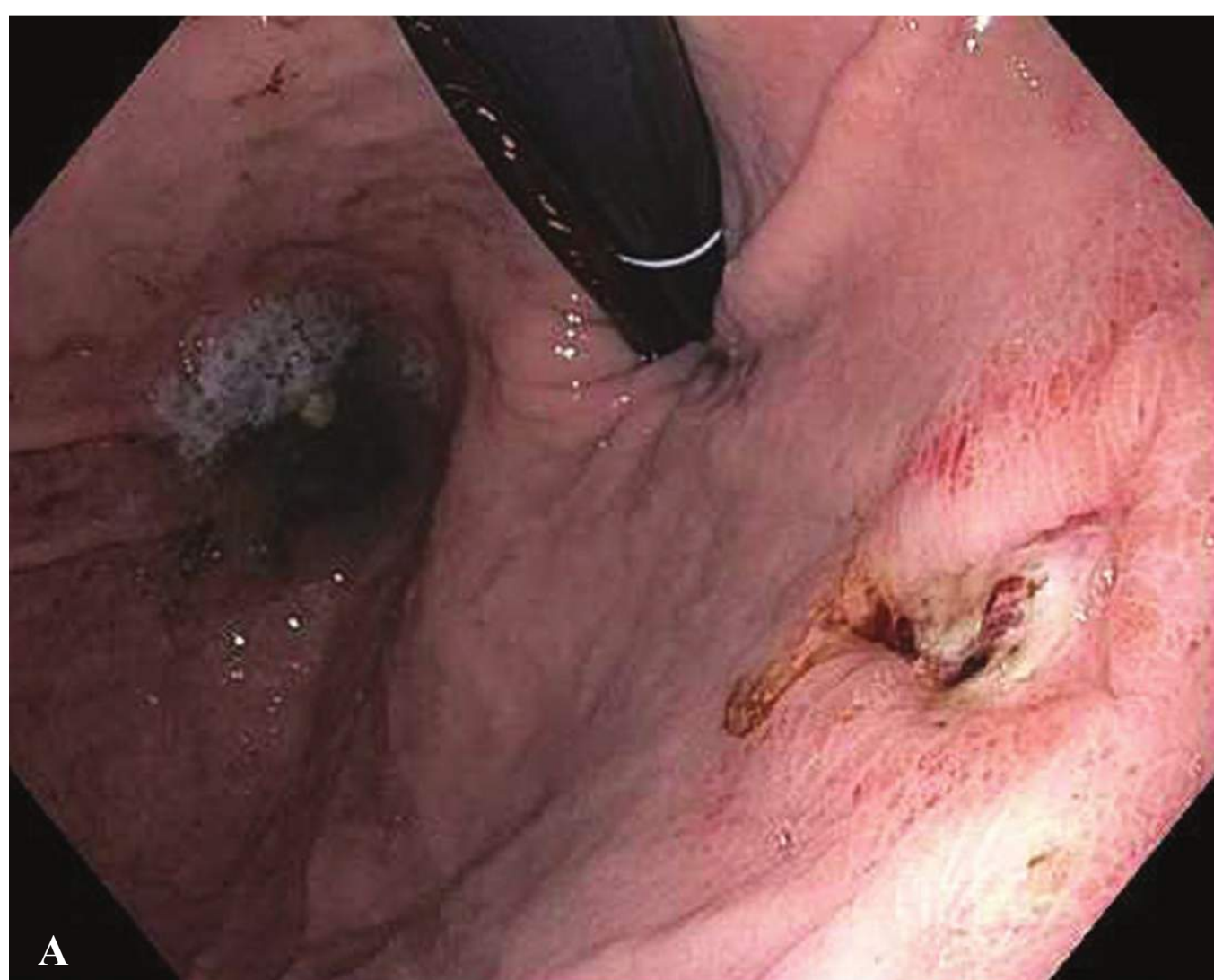


FIGURE 23-2 (A) Stomach ulcer. (B) Peptic ulcer disease.

NSAID use and *H. pylori* infection increases the risk of ulcer bleeding by 4.9- and 1.8-fold, respectively. When present with a history of NSAID use, *H. pylori* has an additive effect and a consequent increase in UGIB risk, with an odds ratio (OR) of 6.13.²⁷

Less common causes of PUD are high-gastrin-secreting states such as Zollinger–Ellison tumors. A history of smoking, alcohol abuse, hepatic failure, and use of medications—including bisphosphonates and selective serotonin reuptake inhibitors—may exacerbate a preexisting ulcer, decrease healing, and increase recurrence and perforation rates.^{28,29}

The patient with PUD classically presents with intermittent burning or gnawing epigastric pain that occurs 1 to 3 hours after meals and is relieved by food and antacid. Constant epigastric pain suggests that there is transmucosal penetration of the ulcer. Referred back pain can be a sign of pancreatic inflammation. Diffuse peritoneal irritation and severe abdominal pain can be signs of perforation. Approximately 5% of penetrating duodenal ulcers will erode into the peritoneal cavity and cause a chemical peritonitis. Typically, the patient can recall the exact time of onset of the abdominal pain, which is frequently accompanied by tachycardia and, later, dehydration, fever, and ileus. Free air under the diaphragm on upright chest radiograph is pathognomonic for perforated viscus. This complication constitutes an emergency, which warrants the initiation of appropriate fluid resuscitation, pain management, and surgical consultation. In general, the elderly are at increased risk for gastric perforation. GI bleeding is the most common cause of death in patients with PUD who have comorbidities or are over the age of 65 years.³⁰

Rebleeding is a common occurrence in patients with PUD because of the acidic environment of the stomach. The acidity promotes mucosal erosion and prevents healing, clot formation, and bleeding control. Rebleeding after endoscopy occurs in up to 20% of cases.¹⁴ In the absence of treatment, the risk of rebleeding is estimated to be between 50% and 90%.² Hypovolemic shock at presentation is associated with poor outcome. Ulcers larger than 2 cm in diameter are at increased risk of rebleeding and mortality.^{2,13} However, early endoscopy and treatment has been demonstrated to reduce the risk of rebleeding and mortality.³¹ PUD is complicated by severe hemorrhage in 19.4 to 57.0 per 100,000 cases and perforation in 3 to 14 per 100,000 cases.¹⁷ The mortality from PUD can be as high as 30% in the elderly population.¹⁴

The prevalence of mucosal erosive disease in UGIB ranges from 1% to 31%, and is a common cause of UGIB. These diseases may present as esophagitis, gastritis, duodenitis, or esophageal ulcer. The pathogenesis and risk factors mimic those of PUD. The lack of standardization in reporting esophagitis and other erosive diseases across study cohorts may explain the wide spectrum of prevalence observed.¹⁹

Stress ulcers, which represent a relevant subset of mucosal erosive disease, deserve particular mention in critical care patients.³² Uncommon in ED patients, stress ulcers are mucosal defects, which are induced during periods of increased physiologic demand and critical illness. Illnesses such as massive burns, trauma, elevated intracranial pressure, sepsis, and

severe shock are all causes of stress ulcers. Endoscopic studies have demonstrated that ulcers are present in 10% to 25% of ICU patients upon admission and in up to 90% of ICU patients three days later.³³ The pathogenesis of stress ulcer formation is unclear, but stress ulcers are generally thought to be caused by splanchnic hypoperfusion and poor reperfusion due to sympathetic nervous system activation, vasoconstriction, and catecholamine release.³³ The concomitant reduction in bowel motility and mucosal secretion of protective substrates are contributory. The increased acidic environment promotes the progression of these superficial diffuse changes to ulcerative lesions. Unlike PUD, *H. pylori* plays a limited role in stress ulcers. Patients presenting with stress ulcers may be distinguished from the typical ED presentations of PUD by the following risk factors: profound persistent hypotension or shock, high-dose vasopressor use, chronic mechanical ventilation, severe burns, uremic renal failure, greater than 6 days of nasogastric tube placement, acute central nervous system (CNS) illness, and high-dose steroid utilization.³⁴ Stress ulcers typically heal when the underlying clinical condition is addressed. Variants of stress ulcers include Cushing and Curling ulcers.

Hemodynamic resuscitation is paramount (see Resuscitation section). Treatment with a PPI is now the standard of care for peptic ulcer disease, as PPIs decrease ulcer rebleeding rates.^{14,35} Once the patient has been hemodynamically resuscitated, early esophagogastroduodenoscopy (EGD) should be performed (see Endoscopy and Proton Pump Inhibitors sections). EGD can confirm the diagnosis of PUD and permit endoscopic management to stop bleeding and prevent recurrence. The combination of PPI and EGD decreases the risk of rebleeding as compared to endoscopy alone.¹³

GASTROESOPHAGEAL VARICES

Gastroesophageal varices remain an important cause of UGIB, accounting for 6% to 14% of presentations. Varices place the patient at risk for developing life-threatening bleeding. Moreover, the presence of varices is also related to severity of liver disease; varices are present in 50% of patients with cirrhosis, and variceal bleeding accounts for 50% to 60% of UGIB events in the cirrhotic patient.¹⁹

Gastroesophageal varices are dilated submucosal veins located in the distal third of the esophagus and/or the gastroesophageal junction (Figure 23-3). The sequence of events that lead to variceal rupture begins with increased hepatic resistance (e.g., due to cirrhosis), leading to increased portal blood flow. These two factors produce an increase in the portal pressure, causing dilation of preexisting vessels and the formation of porto-systemic collaterals, such as varices. Repeated increases in portal pressure due to meals, ethanol, exercise, and increased abdominal pressure all cause further dilation of varices. Rupture and bleeding occur when the elastic limit of the vessel wall is exceeded.³⁶

Gastroesophageal varices are a consequence of portal hypertension. Portal hypertension is most commonly caused by cirrhosis, the end stage of liver disease. The most common causes of liver disease include viral hepatitis, alcoholic cirrhosis, and

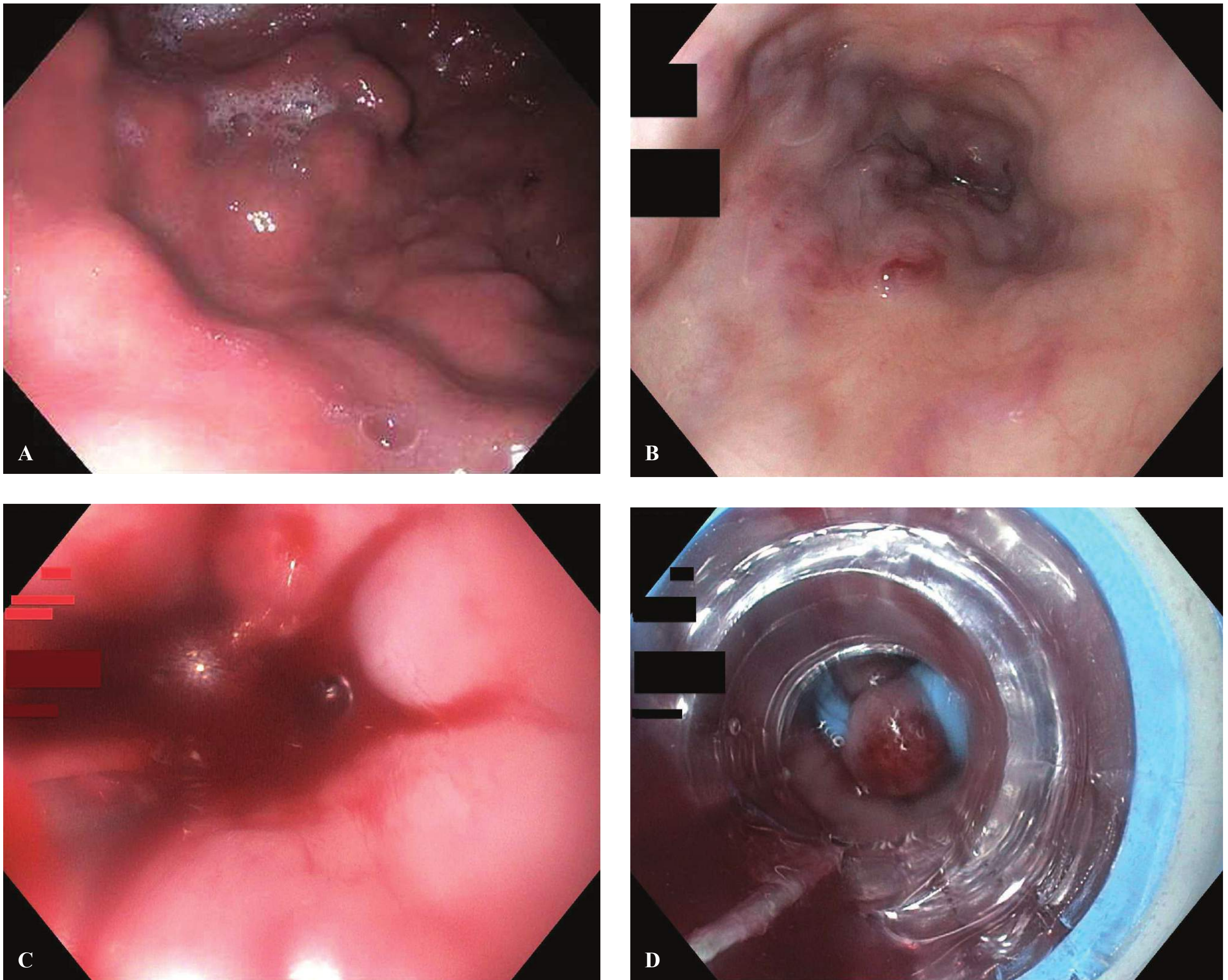


FIGURE 23-3 Endoscopy is the diagnostic and therapeutic modality of choice for UGIB. In esophageal variceal bleeding, mechanical, thermal, or chemical ligation can facilitate hemostasis during emergent endoscopy. **(A)** Gastric varices. **(B)** Esophageal varices. **(C)** Bleeding varix. **(D)** Bleeding varix banding.

nonalcoholic steatohepatitis. Other causes of cirrhosis include autoimmune, drug-induced, and toxin-induced hepatitis. Portal hypertension can also be caused by portal vein thrombosis. Populations with high ethanol consumption observe higher rates of liver cirrhosis and, therefore, higher rates of esophageal variceal bleeding.

Patients with UGIB associated with esophageal varices often present with hematemesis, the vomiting of bright red blood. Not infrequently, patients may have large-volume hematemesis that portends a GI emergency. The patient may or may not have a history of known esophageal varices. Patients may have stigmata of chronic liver disease, including ascites, caput medusae, spider angiomas, palmar erythema, jaundice, gynecomastia, and hepatic encephalopathy.

Variceal bleeding is the most lethal consequence of liver cirrhosis. Bleeding is characteristically severe and is associated with an inpatient mortality of 11% to 34%.³⁷

Although bleeding from varices stops spontaneously in 40% of patients, mortality remains around 20% at 6 weeks despite advancements in treatment.^{38–40}

The management of variceal bleeding is multifaceted. As with all patients, stabilization is a first priority (see Resuscitation section). In large-volume hematemesis, a definitive airway is mandatory. Early GI service consult and rapid diagnostic EGD with band ligation for esophageal varices and tissue adhesives for gastric varices should be performed as soon as possible. Erythromycin infusion should be given before endoscopy, which has been shown to improve visibility during EGD, thereby significantly shortening the procedure time.^{41,42} About 50% of patients treated with erythromycin will have a completely empty stomach during EGD.⁴² Volume replacement with crystalloid is a mainstay of treatment, moving quickly to blood product administration if the patient remains hypotensive or shows evidence of

end-organ hypoperfusion. The literature supports administration of blood products to achieve a mean arterial pressure (MAP) of 65 mm Hg. Plasma and Factor VIIa administration can be harmful by increasing portal pressure, and attempting to correct coagulopathy in a patient with liver disease is not recommended. Intravenous vasopressin should be administered as quickly as possible if hepatic portal hypertension is the suspected cause of major bleeding. Vasopressin offers direct splanchnic and systemic vasoconstriction, decreasing portal venous pressure, thereby decreasing variceal bleeding.^{43,44} Vasopressin should be continued for 3 to 5 days after hemostasis.⁴⁵ Antibiotic prophylaxis with a third-generation cephalosporin or fluoroquinolone should be given to all cirrhotic patients with variceal bleeding for a duration of 5 to 7 days.⁴⁵ In high-risk cirrhotics with continued variceal bleeding, TIPS procedure within 72 hours has been shown to reduce mortality.^{45,46}

MALLORY–WEISS SYNDROME

Mallory–Weiss (MW) syndrome accounts for 2% to 7% of cases of UGIB.^{4,8,47} The pathogenesis of MW syndrome is not completely understood, although any disease that causes retching or vomiting can induce MW. Alcoholism is the most frequently associated condition, although eating and coughing disorders, pregnancy, heavy lifting, diabetic ketoacidosis, and blunt abdominal trauma have all been described.^{48,49} Linear tears, thought to occur as a result of a transient high transmural pressure gradient across the region of the gastroesophageal junction, characterize MW syndrome. Overdilation of the noncompliant lower esophagus can also produce an injury as described in postcardiopulmonary resuscitation patients.⁵⁰ There is a 0.07% to 0.49% incidence of MW syndrome as an iatrogenic consequence of gastroesophageal endoscopy.^{51,52} The presence of a hiatal hernia may be a predisposing factor for MW syndrome. It has been proposed that, in hiatal hernia patients, a higher pressure gradient develops in the hernia compared with the rest of the stomach during retching, thereby increasing the potential for mucosal laceration.⁵³ MW syndrome–induced tears typically result in mild to moderate GI bleeding, but are rarely severe in nature. These superficial mucosal tears tend to heal rapidly and are often self-limited. Bleeding spontaneously stops in about 90% of cases, although coagulopathy or preexisting comorbidities, such as thrombocytopenia and liver failure, can result in refractory bleeding.⁵⁴ Low admission hematocrit (HCT), shock, or active bleeding during endoscopy is predictive of a complicated course.^{55,56}

VASCULAR ANOMALIES

Vascular anomalies or angiodysplasia account for about 2% to 5% of acute UGIB. Upper GI angiodysplasia occurs most commonly in the stomach and rarely in the duodenum or esophagus. Bleeding from angiodysplasia is associated with advanced age; aortic stenosis; chronic renal failure; and calcinosis, Raynaud phenomenon, esophageal dysmotility, sclerodactyly, and telangiectasia (CREST) syndrome.

OTHER CAUSES OF UGIB

Leiomyomas and gastrointestinal stromal tumors (GIST) constitute about 1% of primary GI tumors, mostly occur in the stomach, and often present with overt UGIB. Adenocarcinoma is the most common primary GI malignancy. It presents as a gastric mass, nonhealing ulcer, or stricture. Gastric lymphomas constitute about 5% of gastric tumors. Specifically, gastric mucosa-associated lymphoid tissues (MALToma) are early B-cell lymphomas highly associated with chronic *H. pylori* infection. They rarely cause acute bleeding. Gastric metastases most commonly arise from lung cancer, breast cancer, and cutaneous melanoma. These malignancies frequently rebleed and have a poor long-term prognosis. Radiation and chemotherapy treatment for gastric malignancies can result in UGIB that is difficult to manage and usually requires a multidisciplinary approach.⁵⁷

LOWER GASTROINTESTINAL BLEEDING

Epidemiology

LGIB accounts for 20% of GI bleeding and about one quarter to one third of all admissions for GI bleeding.^{58,59} The incidence of acute LGIB is estimated at 20 to 27 cases per 100,000 adults at risk, which is significantly lower compared with UGIB, which has an incidence of 100 to 200 cases per 100,000 adult population.^{60,61} The incidence of LGIB increases with age and is higher in men, presumably because of the increased frequency of vascular disease and diverticulosis in older men. LGIB is more common in the elderly because of the increased incidence of GI disease in elderly patients (e.g., diverticulosis, vascular ectasias, ischemic colitis, neoplasms), presence of comorbid conditions (e.g., diabetes, cardiovascular disease, cirrhosis, renal disease, hypertension), and polypharmacy (e.g., NSAIDs and anticoagulants).⁶¹ Mortality rates of acute LGIB are consistently in the range of less than 5%.

Clinical Presentation

LGIB is defined as hemorrhage that arises distal to the ligament of Treitz and encompasses a broad clinical spectrum that ranges from minor hematochezia to severe hemorrhage with shock.⁶² Acute LGIB is defined as bleeding of less than 3 days' duration. Severe hemorrhage is defined as a decrease in HCT by 20% or a transfusion requirement of ≥ 2 units of blood. LGIB often presents as hematochezia, melena, dark red blood with clots, or occult bleeding. Although 10% to 15% of hematochezia presentations are from a UGIB source, hematochezia is a common presentation of LGIB.⁶³

Melena, or dark, tarry, foul-smelling stool, suggests a source of bleeding proximal to the cecum, possibly from an upper GI source. Dark red blood with clots suggests an ascending colonic source of bleeding. Occult bleeding is usually not apparent to the patient; however, it is the most common presentation of LGIB in the elderly. Patients can lose up to 100 mL of blood per day and still have stools that appear

normal. Occult bleeding is usually detected with stool guaiac testing; therefore, a digital rectal examination is required for suspected GI bleeding.

Because of the association of LGIB with the elderly, the clinician must be astute; the symptoms of LGIB may not be readily apparent to the patient or to the clinician. Abdominal pain with cramps or tenderness may indicate colitis; however, abdominal pain may not be present in patients taking NSAIDs. Vital signs, especially orthostatic changes, can indicate loss of up to 40% of the circulatory volume. Other clinical data associated with severe bleeding include a heart rate higher than 100 beats per minute, syncope, systolic blood pressure ≤ 115 mm Hg, nontender abdominal examination, anticoagulant use (including NSAIDs and antiplatelet and antithrombotic medications), rectal bleeding during the first 4 hours of evaluation, and more than two active comorbid conditions.⁶⁴

The elderly do not tolerate acute blood loss well; consequently, LGIB may present with clinical manifestations other than hematochezia, including dyspnea, anemia, syncope, and fall, diaphoresis, encephalopathy, myocardial strain or infarction, cerebrovascular accident, or fatigue.

Etiology

The most common etiologies of LGIB will be discussed by order of frequency. A list of causes of LGIB is included in Table 23-2.

DIVERTICULAR DISEASE

Diverticular diseases are the most common cause of significant and life-threatening LGIB in Western populations, accounting for 50% of cases.^{63,65} Although uncommon in patients under 40 years of age, diverticulosis is present in 40% of patients over 60 years old. Anywhere from 10% to 25% of those with diverticulosis will develop symptomatic diverticulitis.

Diverticula develop in the colon where the vasa recta (intramural branches of the marginal artery supplying the colon) penetrate the colonic wall.⁶⁶ They most frequently occur in the left colon, but can exist anywhere in the colon except the rectum. Approximately 50% of LGIB due to diverticula is right colonic in origin.⁶⁷ Abnormal colonic motility, defective muscular structure, increased cross-linking of collagen, and aging are all causes of diverticula. In addition, a diet low in fiber can lead to firm, small stools, which cause reduced

transit time. Over time, vigorous contractions in the colon push the inner intestinal lining outwards through vulnerable points in the muscle walls.⁶⁸ High intraluminal pressure and a weak colonic wall at the sites of vessel penetration into the muscularis lead to herniation.⁶⁹ The pouches that subsequently develop are called diverticula. Diverticular hemorrhage is thought to occur when the damaged vessel ruptures at the dome or the neck of the diverticulum.⁶⁷

A rare disease before the 1900s, diverticulitis is now common in industrialized societies with a Western diet. This is thought to be due to many changes in the diet of industrialized nations but, most important, a decrease in dietary fiber. Other risk factors include advanced age, lack of physical activity, smoking, chronic use of NSAIDs, and caffeine intake.⁷⁰

Diverticulitis typically presents in older adults. The patient may have a history of diverticulosis noted on screening colonoscopy. The most common presentation of diverticular bleeding is massive, painless rectal hemorrhage. The patient may present with signs and symptoms of blood loss, including pale skin, diaphoresis, mental status changes, hypotension, and tachycardia.

Diverticular bleeding resolves spontaneously in approximately 80% to 90% of patients.⁶⁷ Severe blood loss is noted in 3% to 5% of patients with diverticulosis. Patients who present with acute diverticular bleed have a 4% mortality rate.⁷¹ Predictors of increased mortality include age over 70, intestinal ischemia, comorbidities, coagulation defects, hypovolemia, transfusion of packed red blood cells, and male gender.⁷¹

Treatment of LGIB begins with stabilization and resuscitation. Blood products should be used if massive bleeding is present, sometimes requiring use of a massive transfusion protocol (see Blood Product Administration section). The GI service and acute care surgery team should be involved as soon as possible. In patients with bright red blood per rectum, colonoscopy should be performed within 12 hours. If a bleeding site is located during colonoscopy, hemostasis should be performed during colonoscopy. With massive hematochezia, emergent abdominal CT angiography should be performed to locate the source of bleeding and possible area of embolization. If an area of bleeding is not detected, a colonoscopy (with bowel preparation) should be performed as soon as possible. Some patients may present with blood loss so massive that surgery is the preferred method of locating and controlling ongoing blood loss. Surgery may also be indicated in ongoing bleeding with an unknown source, despite endoscopy and CT.⁴⁵



TABLE 23-2: Causes of Lower Gastrointestinal Bleeding

Upper GI bleeding	Diverticulosis	GI carcinoma
Angiodysplasia	Arteriovenous malformation	Mesenteric ischemia
Ischemic colitis	Meckel's diverticulum	Hemorrhoids
Infectious colitis	Dieulafoy lesions	Polyps
Radiation colitis	Rectal ulcers	Trauma
Foreign bodies	Prostate biopsy	Endometriosis
Inflammatory bowel disease	Colonic varices	Portal hypertensive enteropathy

ARTERIOVENOUS MALFORMATIONS

Arteriovenous malformations (AVM) of the intestine, also known as angiodysplasias or vascular ectasias, account for up to 12% to 40% of LGIB.^{61,72} AVMs are found in patients older than 50 years of age and are distributed equally between genders. AVMs have been noted in over 25% of asymptomatic individuals over the age of 60 and are the most common source of occult GI bleeding.^{73,74} Approximately 40% to 60% of patients will have multiple lesions; in 20% of patients, these lesions can be simultaneously located in different areas of the GI tract.⁷⁵

The exact mechanism of AVM development is not fully known. It has been suggested that their development is related to age and strain on the bowel wall,⁴⁵ and chronic venous obstruction is proposed to play an important role. When applied to the bowel lumen, the Laplace law states that tension is highest in bowel segments with the greatest diameter, such as the right colon.⁷⁶

Repeated episodes of colonic distention are associated with transient increases in lumen pressure and size. Over time, this process causes gradual dilation of the submucosal veins, the venules, and the arteriolar capillary units feeding them, resulting in degeneration of previously normal blood vessels. Ultimately, the capillary rings dilate, the precapillary sphincters lose their competency, and a small arteriovenous communication forms.⁷⁷

On histologic examination, these vessels appear to be ectatic and distorted. The right colon has the largest luminal diameter and the highest resting wall tension; therefore, the hemorrhage tends to arise from the right side of the colon, with the cecum being the most common location. However, AVMs can occur anywhere in the colon, rectum, and small bowel.

Although up to 15% of patients with AVM can present with massive life-threatening hemorrhage and hemodynamic instability, patients with AVM typically present with painless, episodic, self-limited GI bleeding, resulting in chronic occult bleeding and iron deficiency anemia.^{2,78,79} Symptoms may include fatigue, dyspnea (especially with exertion), and generalized weakness. Due to the chronic, intermittent nature of vascular ectatic bleeding, a negative guaiac examination does not preclude GI bleeding. The elderly are at increased risk for developing AVMs, and a link between deficiency of high-molecular-weight multimers of von Willebrand factor, aortic stenosis, and colonic angiodysplasia (Heyde syndrome) has also been proposed.^{13,76} These lesions are notably associated with renal failure, especially in elderly patients.

AVMs frequently occur in multiple areas throughout the GI tract simultaneously, creating a therapeutic challenge. In the setting of occult GI bleeding, vascular ectasias found on endoscopic evaluation should be treated. Argon plasma coagulation, electrocoagulation, and mechanical hemostasis are common endoscopic treatment modalities.^{2,80,81} However, AVMs can be missed on colonoscopy due to small size, blood clots obscuring the lesion surface, or hypotension that decreases lesion perfusion. Subsequent angiography can help localize and treat these lesions, but angiographic complications limit its use to patients with life-threatening bleeding

that are not candidates for surgery. Surgical resection is definitive therapy for culprit lesions that have been clearly identified as the source of bleeding. However, rebleeding is common despite treatment for AVM due to the variable and multicentric nature of these lesions. Postendoscopy rebleeding is present in 20% to 34% of patients, and postsurgical recurrent bleeding has been observed in 38% of patients.^{75,82} Recurrence of iron deficiency anemia and the need for repeat transfusion within three years occurs in 16% to 64% of patients. In such cases, medical therapy is an option. Early case reports suggested that hormonal treatment with estrogen and progesterone were effective in treating AVMs, although a subsequent double-blinded, multicenter, randomized controlled trial failed to demonstrate efficacy.⁸³ A meta-analysis of prospective observational studies showed that a significant number of patients with recurrent bleeding responded to octreotide.⁸⁴

ISCHEMIC COLITIS AND MESENTERIC ISCHEMIA

Ischemic colitis causes 3% to 9% of LGIB presentations in the elderly and is the most common cause of GI ischemia, accounting for 50% to 60% of all ischemic bowel cases.⁸⁵ Ischemic colitis occurs with an incidence of 4.5 to 44 cases per 100,000 patient years and accounts for 1 in 2,000 hospital admissions.⁸⁶ Mesenteric ischemia, on the other hand, remains rare (2 to 3 cases per 100,000 population).⁸⁷ Both diseases typically affect the elderly, with patients over the age of 60 accounting for 90% of colitis cases.

The overall prognosis of ischemic colitis is related to its location and whether the patient has comorbid conditions and requires surgery; overall, ischemic colitis has a 22% mortality rate. Patients who have mild symptoms will completely recover within 2 weeks as the colonic mucosa heals. The 20% of patients who require surgery have a mortality rate of 10% to 65%, and patients with pancolitis have a 75% mortality rate.⁸⁶ Transient recurrent colitis can also result in colonic strictures.

The development of bowel ischemia is related to age; increasing age predisposes the patient to other associated comorbidities, including atherosclerosis, arrhythmias, decreased cardiac output, valvular disease, and myocardial infarction (MI). Atherosclerosis of the bowel vasculature reduces baseline mesenteric blood supply. Any additional insult, be it an occlusive or nonocclusive event, can result in temporary or complete occlusion of the vascular supply, causing bowel ischemia and necrosis. Occlusive ischemia is usually a result of thromboembolic disease from valvular heart disease, atrial fibrillation, or cardiomyopathy. Nonocclusive events include hypotension (e.g., caused by shock or dehydration, in which vasoconstricted bowel vasculature redirects blood flow to vital organs), vasculitis, or vasoconstriction (i.e., secondary to exogenous sympathomimetic drugs such as vasopressors or cocaine). The watershed areas of the colon, the splenic flexure and the rectosigmoid junction, are areas with few collaterals and are particularly susceptible to nonocclusive events.

The severity of the resultant necrosis depends on the extent and duration of ischemia. Mild ischemia can result in muco-

sal and submucosal edema, nongangrenous ulceration, and hemorrhage. Severe necrosis can appear similar to inflammatory bowel disease (IBD) with ulcerations, gangrenous transmural infarctions, and strictures.⁶¹ The resultant necrosis causes mucosal sloughing and bloody diarrhea. Mucosal injury occurs within approximately 20 minutes to 1 hour of hypoperfusion, whereas transmural infarction occurs after 8 to 16 hours.⁸⁶ Additional injury occurs when perfusion is reestablished, causing reperfusion injury. Due to the ischemic nature, the bleeding is usually limited; significant LGIB is unusual and should prompt an evaluation for an alternative diagnosis.

Patients with bowel ischemia tend to have multiple risk factors for cardiovascular disease, such as age over 65 years, cardiac dysfunction or arrhythmia, hypertension, renal failure, diabetes, and thrombophilia (e.g., caused by neoplasm, hypercoagulable conditions, or pancreatitis). Chronic obstructive pulmonary disease (COPD) increases the risk of ischemia by two- to fourfold. Constipation increases intraluminal pressures, compressing the mucosal blood vessels. Other risk factors include sickle cell disease and vasculitis.^{86,87}

Ischemic colitis presents with acute-onset abdominal cramping and pain with the urge to defecate and the development of hematochezia, nausea, vomiting, diarrhea, and abdominal distention. The abdomen will be tender over the ischemic portion of the bowel. Development of peritoneal signs indicates advanced progression and transmural necrosis. Patients will typically have signs and symptoms of sepsis, including tachycardia, fever, and leukocytosis. Mesenteric ischemia presents with abdominal pain out of proportion to examination. Patients may have prodromal symptoms, including food fear, worsening colicky abdominal pain, and weight loss. As the disease process progresses to perforation, physical exam signs consistent with peritoneal irritation include rebound, guarding, and abdominal rigidity.

Plain films of the abdomen are rarely helpful for diagnosis, unless perforation causes pneumoperitoneum; otherwise, subtle findings such as thumb-printing or pseudotumors due to submucosal edema may be present. Computerized tomography is the most helpful diagnostic study when performed with intravenous contrast; imaging may demonstrate bowel wall thickening, stranding, submucosal edema, emboli, or thrombi.

The patient should be rapidly resuscitated to restore tissue perfusion and oxygen delivery; volume resuscitation, supplemental oxygen, and initiation of broad-spectrum antibiotics are essential first steps. Additionally, bowel rest, nasogastric tube decompression in the event an ileus develops, and invasive hemodynamic monitoring should be initiated, if applicable. If vasopressors are required, dobutamine and milrinone are preferred, as they have less effect on mesenteric vasculature.

Segmental nongangrenous ischemic colitis (80%–85% of ischemic colitis cases) often resolves with maximal medical management. However, the remaining gangrenous cases require surgical resection. For mesenteric ischemia, treatment depends on the etiology. For arterial emboli, the treatment of choice is open surgical embolectomy to remove the clot and evaluate bowel viability. For the management of acute-on-chronic mesenteric ischemia, open thrombectomy with

endarterectomy or distal bypass are the treatments of choice. Mesenteric venous thrombosis is treated with systemic anticoagulation.^{86,87}

AIDS/HIV

Patients with HIV/AIDS may have unique etiologies of GI bleeding compared with uninfected cohorts. AIDS is defined as a CD4⁺ T cell count of less than 200 or the presence of AIDS-defining illness, such as pneumocystis jiroveci pneumonia (PJP), cytomegalovirus disease, and toxoplasmosis. Sources of UGIB, although most often unrelated to HIV, may include cytomegalovirus (CMV) and Kaposi sarcoma. Conversely, LGIB affects approximately 3% of patients with AIDS; around 70% of these cases result from HIV infection.⁸⁸ HIV-related LGIB is typically a result of immunodeficiency. HIV is associated with an increased risk of infection as well as an increased risk of lymphoid malignancies.⁸⁹ The most common causes of LGIB in patients with HIV/AIDS are CMV colitis, lymphoma, and idiopathic colitis.^{90,91} CMV colitis occurs in over 7% of all patients with AIDS, although few patients with CMV colitis (approximately 9%) present with GI bleeding.^{92,93} Non-Hodgkin lymphoma is found in 4% of HIV-positive patients, and there is endoscopically confirmed GI involvement in 45% of those patients.⁹⁴ Because of concomitant thrombocytopenia, patients with HIV may present with serious bleeding from an otherwise self-limiting source, such as hemorrhoids and anal fissures.^{88,91} In HIV patients with LGIB, CMV colitis typically presents with abdominal pain, bloody stool, diarrhea, and fever, although not all have to be present to consider the diagnosis.⁹⁵ Lymphoma typically presents with B symptoms, including weight loss, fever, night sweats, and painless, swollen lymph nodes.

Initial management of LGIB in patients with HIV/AIDS is the same as patients without HIV infection. The initial task is stabilization and resuscitation. Next, the source of bleeding should be identified.⁹¹ Most causes of LGIB in patients with HIV can be diagnosed through endoscopy, some by the characteristic appearance, and others by biopsy.^{91,95,96} Colonoscopy with ileoscopy is preferred, and sigmoidoscopy should not replace colonoscopy.⁹⁵ Ganciclovir should be used to treat CMV colitis. The patient should be started or continued on antiretroviral therapy. Lymphoma is treated similarly to lymphoma in patients without HIV.

Rebleeding occurs in 17% to 22% of patients.^{88,90} In patients with HIV, there is a 14% to 28% 30-day mortality rate for patients presenting with LGIB.^{88,90} However, this high mortality is due to AIDS-related comorbidities and not directly to blood loss.⁹⁰

OTHER CAUSES OF LGIB

Aortoenteric fistulas can cause LGIB. They are abnormal connections between the aorta and the GI tract that are a rare consequence of prior aortic surgery, aortic aneurysms, and severe atherosclerosis. They occur in 0.5% of patients who have previously undergone aortoiliac surgery or endovascular repair. These fistulas can present with native anatomy or

after stent placement. The median time interval from aortic surgery or repair to development of an aortoenteric fistula is 90 months.^{13,97}

Patients often present with a mild sentinel hemorrhage or “herald bleed” followed by massive, exsanguinating hemorrhage that has a high mortality with delayed diagnosis. For this reason, emergency EGD is indicated if this diagnosis is suspected. Aortoenteric fistulas are typically located at the distal duodenum, underscoring the role of endoscopic investigation up to this location. During EGD, if a prosthetic graft mesh is found, the scope should be withdrawn without attempting therapeutic intervention, and the lesion should be treated intraoperatively due to the risk of massive bleeding.^{97,98} CT angiography is another key diagnostic modality of aortoenteric fistulas.

Other less frequent etiologies of LGIB include malignancy, IBD, NSAID use, infectious colitis, anorectal disorders, small bowel sites (i.e., Crohn disease, Meckel diverticulum), and postpolypectomy bleeding.^{58,62,99}

MANAGEMENT OF GASTROINTESTINAL BLEEDING

Careful consideration of the management approach of GI bleeding is needed due to the high morbidity and mortality associated with this condition.^{100,101}

For critical patients, consultation with gastroenterologists and surgeons should occur early in the patient’s course.

Airway and Cardiovascular Considerations

The management of patients with GI bleeding includes initial and ongoing resuscitation. Aggressive replacement of lost volume with crystalloids and colloids is obligatory in hemodynamically unstable patients. Initial resuscitation should begin with the placement of two large-bore intravenous catheters and administration of one to two 20 mL/kg bolus(es) of crystalloid, with the short-term goal of resolution of tachycardia and hypotension to restore tissue perfusion. Refractory hypotension, evidence of end-organ hypoperfusion, or persistent hemorrhage should prompt the administration of packed red blood cells (PRBC) and the consideration of central access and invasive hemodynamic monitoring. Blood administration should not be delayed pending the results of a repeat hemoglobin (Hb) assay or the visualization of hematemesis, melena, or hematochezia in the setting of hemodynamic compromise.

Attention to the airway during massive hemorrhage is crucial. Massive hematemesis can result in a compromised, visibly obscured airway. Manifestations of hemorrhagic anemia may cause decline in mentation and increased aspiration risk. Even more serious are bleeding esophageal varices, resulting in hepatic encephalopathy. Endoscopic interventions in patients with frequent bouts of hematemesis, vomiting, or retching can prove challenging and may lead to further complications. Consequently, the physician should have a low threshold in establishing a definitive airway in the anticipation of potential

cardiovascular compromise and need for therapeutic endoscopic or surgical intervention in the setting of large-volume hematemesis.

Laboratories

In the evaluation of the bleeding patient, blood should be immediately sent for complete blood cell count (CBC), metabolic and electrolyte panels, calcium, renal function, glucose, hepatic function, prothrombin time, partial thromboplastin time, international normalized ratio (INR), and lactate assays, and typed for cross-matched blood. Although low Hb is expected in cases of massive GI bleeding, slow, intermittent bleeds or early presentations can have Hb levels within normal range. In a study in which 51% of UGIB patients ultimately required transfusion, the mean presenting Hb was 11.3 g/dL.¹⁰² Because of the dynamic nature of GI bleeding, Hb and HCT should be serially measured to identify significant changes over time. These changes may or may not be heralded by a disruption in hemodynamics, change in clinical appearance, or symptoms such as chest pain, shortness of breath, or altered mentation. An elevated blood urea nitrogen (BUN) to creatinine ratio is suggestive of an upper GI source.¹⁰² However, rapid transit may preclude the elevation of BUN and present with a normal ratio. The existence of thrombocytopenia or coagulopathic disturbances should prompt judicious correction with platelets, fresh frozen plasma, and/or cryoprecipitate, with the assistance of thromboelastography (TEG). Lactic acid, the byproduct of anaerobic metabolism, is elevated in end-organ ischemia and hypoperfusion from blood loss. However, elevated lactic acid can also result from GI bleeding and liver dysfunction.

Gastric Tubes and Lavage

The placement of a gastric tube to ascertain the existence and severity of a UGIB is controversial. Many studies have failed to demonstrate an improvement in clinical outcome with gastric lavage.^{103,104} However, some practitioners continue to support the use of lavage to evaluate for continued bleeding and to aspirate particulate matter and facilitate endoscopy. There are multiple potential safety issues that should be considered, including aspiration pneumonitis, laryngospasm, and perforation of the pharyngeal and gastrointestinal structures.¹⁰⁵

Contraindications to placement include history of esophageal varices or strictures, recent alkaline ingestion, and a history of gastric bypass surgery. Patients with an altered level of consciousness should be intubated in order to provide airway protection prior to placement of a gastric tube. In the event of maxillofacial trauma, patients should have an orogastric tube placed to avert passing the tube through the cribriform plate. If immediate endoscopy is available, the gastric tube offers little incremental benefit and may be omitted. Room-temperature tap water or saline lavage prior to endoscopy is considered safe and may be a potential adjunct in the management of suspected UGIB from PUD.¹⁰⁶ Ice-water lavage was once considered an acceptable therapeutic intervention

for UGIB via gastric vessel vasoconstriction; however, this is not supported by the literature.¹⁰⁴

The aspiration of fresh blood indicates active bleeding, whereas an aspirate with a coffee-ground appearance is associated with a subacute or chronic etiology of the UGIB. The lack of bloody aspirate does not rule out the possibility of a UGIB.^{107,108}

Coagulopathy

Up to 16% of patients with UGIB have evidence of coagulopathy, defined as an INR of 1.5 or greater, leading to greater severity of bleeding as compared to those without coagulopathy. The presence of coagulopathy increases the risk of in-hospital mortality by fivefold.¹⁰⁹

GI bleeding may result from the use of anticoagulants such as warfarin, heparin, low-molecular-weight heparin; novel oral anticoagulants (NOAC) including dabigatran, rivaroxaban, edoxaban, apixaban; and antiplatelet agents such as aspirin or clopidogrel, or NSAIDs. In addition, a history of clotting factor deficiency or cirrhosis may indicate that a disruption in the homeostasis of the coagulation cascade exists. Therapy should be directed at correcting the underlying etiology in these cases.

Although coagulopathy is a poor prognostic factor for GI bleeding, there is significant clinical uncertainty in regard to the optimal transfusion management, with wide variation in the use of blood products and reversal agents.¹¹⁰ Warfarin toxicity is treated with the administration of 4 to 6 units of FFP. Intravenous administration of 10 mg vitamin K is an adjunct medication that can be used to reverse the effects of warfarin in the setting of life-threatening bleeding; however, its onset of action is delayed and its effect can last 1 to 2 weeks. Reversal of vitamin K antagonists, such as warfarin, should be carefully weighed against the future need to chronically anticoagulate the patient.

The management of patients with GI bleeding who are taking antiplatelet medications has historically been difficult for clinicians. Platelets may be administered to actively bleeding patients with a history of thrombocytopenia, salicylate, or NSAID use. However, the risk of continuing antiplatelet therapy and worsening GI bleeding must be weighed against withholding medication and thromboembolic risk. A large prospective study demonstrated that the strongest predictor of stent thrombosis within 6 months was the discontinuation of clopidogrel.^{14,111} Therefore, the decision to discontinue antiplatelet therapy should be made in consultation with a cardiologist as the clinical situation permits. Cryoprecipitate and individual clotting factors may be administered if appropriate. DDAVP or desmopressin should be considered in patients who present with chronic renal failure or uremia to increase the production of von Willebrand factor, as these patients have poor platelet aggregation.

Factor VII, which is available in a recombinant formulation, complexes with tissue factor and activates factor Xa to induce clot production. It is approved for use in bleeding patients with hemophilia A. In cirrhosis, factor VII administration remains controversial as there are conflicting results

from trials evaluating its use in the management of acute variceal bleeding.¹¹²

Novel agents, such as prothrombin complex concentrate, may serve a future role in massive hemorrhage in patients with a known deficiency of vitamin K or NOAC use, although such agents are contraindicated in patients with disseminated intravascular coagulation (DIC) or liver disease.¹¹² (See the Transfusion in Critical Care chapter.)

TEG assesses the coagulation and fibrinolysis cascade, evaluating the dynamics of clot formation, strength, stability, and lysis. It incorporates plasmatic events as well as cellular components and platelet scaffolding, in contrast to the standard tests of coagulation, prothrombin time (PT), partial thromboplastin time (PTT), and international normalized ratio (INR). Although it has seen significant use in surgery and trauma, more prospective studies are needed for its applicability in GI bleeding.¹¹³

Blood Product Administration

Blood products provide obvious benefits in repleting lost volume, replacing blood components, and correcting acidosis. However, a number of studies have demonstrated that blood product administration has been associated with immunosuppression, increased nosocomial infection rates, and death.¹¹⁴

In addition, transfusion during acute variceal bleeding may reverse the splanchnic vasoconstriction caused by hypovolemia, increase splanchnic blood flow, and impair clot formation, possibly worsening the bleed.¹¹⁵ Thus, it is important to properly select patients who would receive the greatest benefit from blood administration.

Patients exhibiting signs of end-organ hypoperfusion benefit from the additional oxygen-carrying capacity of PRBCs. Findings suggestive of global tissue hypoxia may include altered mental status, seizures, hypoxemia, ischemic electrocardiographic changes, or elevation of lactate, creatinine, hepatic transaminases, or troponin. In the absence of these findings, patients should be transfused according to a restrictive strategy and Hb should be kept at ≥ 7 g/dl in patients without history of coronary artery disease (CAD) and ≥ 10 g/dl in those with a history of CAD.¹¹⁴⁻¹¹⁶ Bleeding patients who require greater than 10 units of PRBC over a 24-hour period are also at risk for the depletion of coagulation factors and platelets because of the dilutional effect. Once the first 10 units of PRBC have been administered, the administration of fresh frozen plasma and platelets should be considered. The precise ratios that would render most benefit are unclear.^{117,118} At the authors' institution, massive transfusions are administered in a 1:1:1 ratio. Patients should also be monitored for volume overload, hypothermia, hyperkalemia, hypocalcemia, and iron toxicity.¹¹²

Medications

PROTON PUMP INHIBITORS AND H₂-RECEPTOR ANTAGONISTS

PPIs act directly at H⁺-K⁺-ATPase channels to interrupt the production of H⁺ ions, whereas H₂-receptor antagonists block

the action of histamine on gastric parietal cells. Both classes of medications function as antisecretory therapies to increase the gastric pH, which promotes the platelet aggregation that is impaired in acidic environments.¹¹⁹ PPIs or H₂-receptor antagonists should be administered intravenously and the patient should be kept NPO.

When compared with placebo or H₂-receptor antagonists, PPIs reduce the risk of rebleeding and the need for subsequent transfusions and surgery in endoscopically diagnosed UGIB from PUD. PPIs, however, have not been shown to reduce the overall mortality from peptic ulcer bleeding, but may reduce the mortality in patients with high-risk endoscopic findings such as active bleeding or a visible vessel.^{2,120,121}

In the setting of NSAID-induced ulcers, PPI therapy has been shown to be more effective in healing and preventing ulcers than H₂-receptor antagonists.¹²² Among critically ill patients, earlier trials suggested no clinically significant difference between PPI and H₂-receptor antagonist use. However, with the advent of intravenous PPIs, a subsequent systematic review demonstrated that PPIs are more effective in preventing clinically important and overt UGIB than H₂-receptor antagonists.^{32,33,123}

PPI treatment prior to EGD reduces the incidence of high-risk stigmata of hemorrhage visualized during endoscopy, including active bleeding, nonbleeding visible vessels, adherent clots, and the need for therapeutic EGD intervention.^{14,124} PPI treatment initiated after endoscopy improves the rate of rebleeding, mortality, and the need for subsequent surgery when compared to placebo.^{14,124}

PPIs remain an important adjunct to endoscopy, as they reduce the need for therapeutic intervention during the procedure.¹²⁵

The optimal dose and route of administration have not yet been clearly elucidated; however, suggested dosing is an initial intravenous bolus equivalent to 80 mg of omeprazole followed by an intravenous infusion of 8.0 mg/h for up to 72 hours, at which point high-dose oral PPI treatment may be initiated.¹⁵

No difference has been observed between oral versus intravenous PPIs in the risk of rebleeding, transfusion requirement, or need for surgical intervention.^{126,127} However, PPI intravenous infusion may allow more sustained elevation in pH, which is desirable as fluctuation in gastric pH allows pepsin activation and clot disruption.

SOMATOSTATIN/OCTREOTIDE

Somatostatin and its analogue, octreotide, are peptides that inhibit the exocrine function of glandular tissue, which reduces both acid and pepsin secretion. Moreover, somatostatin and octreotide reduce gastroduodenal mucosal blood flow that, in concert with the reduction in acid production, should theoretically prove to be of benefit in PUD, although evidence for their role in the management of PUD is lacking.¹²⁸

The role of octreotide in variceal bleeding has been clearly demonstrated to facilitate hemostasis when used in conjunction with endoscopy.^{45,129–132} The recommended regimen includes an initial bolus of 50 mcg followed by an infusion of 50 mcg/h.

VASOPRESSORS

Generally, the use of vasopressors should be discouraged in hemorrhagic shock. Hypotension should primarily be addressed by volume resuscitation with crystalloids and colloids or with blood product administration. The placement of a central line in the internal jugular or subclavian veins can facilitate administration of fluids directly into the cardiac circuit as well as provide guidance in fluid administration via monitoring of the central venous pressure (CVP). A CVP reading below 8 mm Hg may indicate the need for additional volume infusion. Additional data, including lactic acid, pulse pressure variation (PPV), stroke volume variation (SVV), central venous oxygen saturation (ScvO₂), and sonographic assessment of inferior vena cava (IVC) collapsibility can help guide volume resuscitation.

Vasopressin, used commonly in the pre-PPI era, is an endogenous vasopressor normally secreted by the posterior pituitary in response to hypotensive states. It preferentially vasoconstricts splanchnic vessels to reduce portal venous inflow and pressure. In the pre-somatostatin era, vasopressin was frequently utilized in cirrhotic patients who, at an advanced stage of the disease, have an impaired ability to generate systemic vascular resistance. However, vasopressin's lack of selectivity at high doses makes it a less desirable agent. Vasopressin use has been reserved for massive refractory bleeding and is administered intravenously in a dose of 0.1 to 1.0 unit/min. Concomitant intravenous administration of nitroglycerin at 40 to 400 mcg/min can be used to counteract cardiac and bowel ischemic sequela of vasopressin. A synthetic analogue of vasopressin, terlipressin, is used more commonly in Europe, and may have a role in the chronic management of hepatorenal syndrome given its limited side-effect profile and longer half-life.¹³³

In ischemic colitis, further vasoconstriction is undesirable. Contrary to the nonselective nature of vasopressin, dobutamine, low-dose dopamine, and milrinone have less effect on the splanchnic vasculature. These medications produce an inotropic effect and enhance bowel perfusion without adversely affecting the bowel vasculature.

ANTIBIOTICS AND PROKINETIC AGENTS

Up to 50% of hospitalized patients with severe liver disease and GI bleeding are susceptible to bacterial infections, including spontaneous bacteremia, spontaneous bacterial peritonitis, pneumonia, and urinary tract infections. Antibiotic prophylaxis with parenteral cephalosporins (i.e., ceftriaxone) or enteral quinolones (i.e., norfloxacin) is recommended.^{33,134,135} For the management of *H. pylori* infection, PPI-based or ranitidine bismuth citrate-based triple therapy with clarithromycin and amoxicillin or metronidazole for a minimum of 7 days is recommended.^{14,25}

Erythromycin, a macrolide antibiotic, and metoclopramide, a dopamine receptor antagonist, serve as potent gastroprokinetic agents and induce gastric emptying. When administered prior to endoscopy, they improve the quality of endoscopic visualization and, thereby, the ability to provide therapeutic

intervention. Proton pump inhibitors decrease the need for repeat EGD; however, other clinically relevant endpoints—such as hospital length of stay (LOS), need for surgery, or amount of PRBCs transfused—showed no improvements.^{14,42,45}

Special Management Considerations in Hepatic Cirrhosis

Resuscitation and management of the hepatic cirrhosis patient deserves special attention. Varices typically occur in the third to fourth stages of cirrhosis; these patients often preferentially pool their intravascular volume in the markedly vasodilated mesenteric circulation. Thus, persistent hypotension in these patients may be the rule. Markers of adequate resuscitation in these patients are less clear. Lactate may be elevated because of liver compromise. In addition, aggressive fluid resuscitation can raise portal pressures, increasing shear stress against the already compromised varix. Moreover, dilution of coagulation factors in the cirrhotic patient may lead to increased or refractory bleeding.

The use of crystalloids, although initially appropriate, should be limited. The resuscitation strategy should be promptly transitioned to one that utilizes colloid in the form of PRBCs, fresh frozen plasma, platelets, or albumin as needed. Maintaining a systolic blood pressure of 80 to 90 mm Hg may be adequate, provided that the patient is not exhibiting other signs of hypoperfusion.

Approximately 20% of UGIB cirrhotic patients have bacterial infections at admission; 50% subsequently develop infections during hospitalization. Antibiotic administration has been shown to enhance survival in these patients.^{136,137} Quinolones or cephalosporins are recommended for these patients.^{138,139}

Diagnostics and Procedures

BALLOON TAMPONADE

The Sengstaken–Blakemore tube, introduced in the 1950s, is a double-balloon esophageal tamponade system used in life-threatening UGIB from esophageal or gastric varices. The gastric balloon occludes, feeding vessels at the gastroesophageal junction, reducing the pressure in the esophageal varices, while the esophageal balloon provides direct compression.¹⁴⁰

Complications associated with its placement include esophageal or gastric rupture, pressure necrosis, and aspiration pneumonitis. An updated version, the Minnesota tube, has an added esophageal suction port to minimize aspiration. Because of the prohibitively high complication and mortality rate associated with balloon tamponade, exhaustion of medical and endoscopic therapies prior to placement is recommended.¹⁴¹ However, massive refractory hemorrhage that precludes endoscopy or is associated with hemodynamic instability may warrant the placement of a balloon tamponade system.

Prior to insertion of a balloon tamponade system, patients should be mechanically ventilated. The balloons and aspiration ports should be checked for integrity and patency. In

the event that there is no esophageal aspiration port, a nasogastric tube can be sutured onto the Sengstaken–Blakemore tube proximal to the esophageal balloon. The tube should be advanced orally approximately 50 cm into the gastric cavity. The stomach should then be aspirated of its contents. The gastric balloon can then be inflated in increments of 100 mL to a maximum of 400 to 500 mL. The Sengstaken–Blakemore tube should then be placed on a traction device to achieve hemostasis. If bleeding persists, the esophageal balloon may be inflated to 30 to 40 mm Hg. Malpositioning is not uncommon; placement should be confirmed by chest radiograph.^{133,140,142,143} The Linton–Nachlas tube, which has a single distal balloon, may be used only in patients with documented gastric varices.¹⁴⁴

ENDOSCOPY

Early assessment of the etiology and severity of bleeding will dictate further therapy and need for critical care monitoring. Endoscopic management is successful in greater than 75% of patients. However, despite endoscopic therapy, rebleeding occurs in 7% to 29% of cases, and is most common with variceal bleeding. Approximately 15% to 20% of endoscopically treated GI bleeding recurs within 72 hours. Risks associated with endoscopy include aspiration, anesthesia and sedation complications, bowel perforation, and an exacerbation of hemorrhage.²

ESOPHAGOGASTRODUODENOSCOPY

Following adequate resuscitation, EGD is the diagnostic and therapeutic modality of choice for UGIB (depending on the etiology of the bleed) and may be indicated in certain cases of LGIB with unclear etiology. EGD serves a role in diagnosis, triage, and therapy.^{42,145} The benefits of EGD over other therapeutic modalities are decreased rates of further bleeding, fewer blood transfusions, lower mortality, shorter hospital stays, and lower hospital costs.¹⁴⁶

Despite its advantages over other modalities, the timing and value of “early” EGD is unclear; whether EGD is performed within a few hours of presentation or within 24 hours, it has been difficult to demonstrate consistent reductions in rebleeding, hospital LOS, or need for surgery.¹⁴⁷

In PUD, hemostasis can be achieved by injection therapy with epinephrine or an alternative agent, mechanical clipping, or thermal treatment.² The combination of mechanical clipping and chemical injection improves hemostasis and prevents rebleeding when compared to single therapy.¹⁴⁸ Visible vessels or the presence of spurting or oozing blood predict further rebleeding and increased mortality. Almost all fatal rebleeding occurs within the first 24 hours.¹¹⁹

In MW syndrome, the occurrence of shock or active bleeding during endoscopic evaluation is predictive of recurrent bleed and warrants intensive care monitoring.⁵⁵ Sclerotherapy or injection with epinephrine may be of benefit with some MW lesions.

Endoscopic therapy of variceal bleeding may be achieved by sclerotherapy or ligation. The administration of somatostatin

or octreotide early in suspected variceal bleeding facilitates achievement of hemostasis during emergent endoscopy.^{149,150}

The addition of antibiotic prophylaxis in cirrhotic patients appears to also reduce postendoscopic treatment failures. Endoscopy has not been shown, however, to reduce overall mortality in acute variceal bleeding, with rebleeding occurring in 10% to 15% of cases.¹⁵¹

COLONOSCOPY

Colonoscopy is the modality of choice in evaluating LGIB; it is able to detect the location of bleeding in 48% to 90% of patients.² Fifteen percent of patients with clinically significant hematochezia and no clinical evidence of UGIB actually had UGIB on endoscopy. Therefore, patients with hematochezia or hypotension should have upper endoscopy performed first to evaluate for a brisk UGIB.¹⁵²

Although studies have demonstrated that successful colonoscopy can be achieved without bowel preparation, the American Society of Gastroenterology recommends thorough colon cleansing to enhance visualization of occult lesions.¹⁵³

Hemostasis is achieved by thermocoagulation, argon plasma coagulation, injection therapy of various agents, and mechanical methods, including banding. The incidence of complication is 1 in 1,000, with perforation occurring rarely. The diagnostic yield of urgent colonoscopy is high if performed within 12 to 24 hours of presentation, although it may not necessarily reduce mortality, transfusion requirement, or LOS.¹⁵⁴ Evidence of active bleeding, visible vessels, or adherent clot during colonoscopy is associated with a complicated course and rebleeding.¹⁵⁵

CAPSULE ENDOSCOPY

Five percent of GI bleeding is not localized with traditional endoscopy; a significant proportion of these cases are due to small-bowel lesions, such as AVM, ulceration, neoplasm, or varices.¹⁵⁶ Traditional endoscopy has a poor duodenal visualization rate of 48% to 58% despite the use of pre-endoscopy gastroprokinetic agents and adequate bowel preparation.^{157,158} Capsule endoscopy employs a swallowed camera that transmits images of the GI tract not visualized by traditional endoscopy. It improves the diagnosis of obscure GI bleeding with a diagnostic yield of 58% to 84%.¹⁵⁹ This modality has been demonstrated to be feasible in the ED setting.¹⁶⁰ However, limitations include a lack of therapeutic utility, the potential for missed lesions, and a limited field of view of 140°.¹⁵⁹

Diagnostic and Interventional Radiology

ANGIOGRAPHY

Formal peripheral angiography has the capacity to identify a lesion that is actively bleeding at a rate of 0.5 to 1.0 mL/min. Advantages of angiography include the ability to identify the precise location of the bleed and the potential for a therapeutic intervention via embolization. Disadvantages include an inability to identify venous bleeding and a major complication rate of up to 9.1% associated with contrast administration,

femoral artery thrombosis, and transient cerebral ischemic events.¹⁶¹

Embolization can be used for UGIB lesions, particularly in the case of active massive bleeding that precludes the performance of endoscopy. Embolization in this setting rarely causes ischemia and has the advantage of averting surgery, but is associated with rebleeding in up to 30% of cases.^{162,163}

Angiography is indicated in patients with persistent recurrent LGIB without an identified source on endoscopy or with active massive bleeding that again precludes the performance of endoscopy. If identified during angiography, most LGIB is amenable to embolization with a high success rate. In the event that hemostasis is not achieved, the interventionalist may inject methylene blue at the bleeding site to facilitate a subsequent intraoperative surgical approach.¹⁶³

Multidetector CT angiography is equivalent to peripheral angiography in its ability to detect the site of active bleeding and is increasingly used for this purpose.¹⁶⁴ It can detect active bleeding at a rate of 0.3 mL/min with high sensitivity and specificity. Advantages of this approach include its minimally invasive nature, rapid speed, wide anatomical coverage, and ability to localize active bleeding for subsequent therapeutic modalities. Limitations include poor visualization of intermittent GI bleeding, radiation exposure, possible contrast allergic reaction, and lack of therapeutic utility.^{59,61}

BLEEDING SCAN

Nuclear scintigraphy with ^{99m}Tc-labeled red blood cells or ^{99m}Tc-sulfur colloid is indicated in patients who have an occult or intermittent source of LGIB that is undetected by endoscopy or angiography. It has the advantage of increased sensitivity compared with angiography and is able to detect bleeding at a rate of 0.1 to 0.5 mL/min.⁶¹ Significant drawbacks to nuclear scintigraphy are that the radioactivity has a long half-life and can be detected on delayed imaging 24 hours later and that overlapping segments of bowel and migration of labeled red blood cells in the intestine may cause significant artifacts; therefore, its accuracy in localizing the bleeding source rapidly declines 2 hours after study initiation.^{2,165}

TIPS

Endoscopic treatment failures in the management of esophageal varices require transjugular intrahepatic portosystemic shunt (TIPS). The right hepatic and portal veins are accessed percutaneously via the right internal jugular vein. A cannula is then inserted to create a portosystemic communication to reduce portal pressures. In high-risk cirrhotics with continued variceal bleeding, the TIPS procedure within 72 hours has been shown to reduce treatment failure and mortality.^{45,46} Complications include worsening liver function, hepatic encephalopathy, and pulmonary hypertension.¹⁶⁶

TIPS is often used as a bridge to liver transplantation or for palliation in advanced-stage cirrhosis.¹⁶⁷ Contraindications include severe hepatic failure, hepatic encephalopathy, polycystic liver disease, right-sided congestive heart failure (CHF), malignancy, sepsis, and severe coagulopathy.¹⁶⁸

Surgery

UGIB

The advent of PPIs and therapy for *H. pylori* infection have greatly reduced the need for surgical intervention in bleeding PUD.⁹¹ The classic indications for surgical intervention for patients with refractory bleeding despite medical or endoscopic therapy include loss of 30% of the estimated blood volume in the first 24 hours, a requirement of greater than 1,500 mL of transfused blood per 24 hours to maintain stable hemodynamics, hemorrhage to the point of hypotension or shock, and recurrent bleeding during medical therapy.¹⁰¹

Other indications include torrential bleeding from large gastroduodenal ulcer, posterior duodenal bulb ulcer with visible vessel, aortoduodenal fistula, or tumor necrosis.^{2,31} A mortality rate of up to 25% is observed in patients who require surgery. Repeat endoscopic therapy, however, has been shown to reduce the need for surgical intervention without increasing mortality.¹⁶⁹ Moreover, when compared with surgery, angiographic embolization appears to be equally efficacious and is associated with lower morbidity.¹⁶³

LGIB

LGIB lesions that are not amenable to endoscopic intervention or angiographic embolization, such as neoplasms, should be considered for surgery. Because intraoperative identification is not feasible, preoperative localization of the bleeding lesion is necessary to prevent blind resection of bowel segments. Blind resection is associated with very high rebleeding (47%) and mortality (25%–57%) rates, thus should be reserved only for severely unstable patients for whom immediate life-saving surgery is the only option.⁶¹ Surgical resection is necessary in up to 24% of patients with recurrent diverticular bleeding, but should be used as a last resort.⁶¹

RISK STRATIFICATION

Predicting the outcome of patients with GI bleeding from their initial presentation can be made easier by employing one or more scoring systems to risk stratify and help decide treatment options. A few different scoring systems have been established that can be used to evaluate patients with GI bleeding. The Glasgow–Blatchford risk stratification scoring system for GI bleeding can be used to predict the need for treatment of patients who present with UGIB. Patients with UGIB may be safely discharged if they meet the following criteria: Hb greater than 12.9 g/dL in men or 11.9 g/dL in women; a systolic blood pressure greater than 109 mm Hg; pulse less than 100 beats/min, BUN level less than 18.2 mg/dL, no melena, no history of syncope, and no past or present liver disease or heart failure.¹⁷⁰ A simpler version of the score, known as the Modified Glasgow–Blatchford score, performs as well as the full Glasgow–Blatchford score, and is calculated using only BUN, Hb, systolic blood pressure, and pulse.¹⁷¹ However, although many studies have found the Glasgow–Blatchford scoring system useful for ED populations,^{172,173}

other studies have determined that it is not sufficiently reliable for use in clinical practice.¹⁷⁴

AIMS65 is another scoring system that was derived to assess inpatient mortality risk among patients with UGIB. AIMS65 found five factors associated with increased inpatient mortality: albumin less than 3.0 g/dL, INR greater than 1.5, altered mental status, systolic blood pressure of 90 mm Hg or less, and age over 65 years. Mortality increases significantly as the number of risk factors increase; zero risk factors are associated with a 0.3% inpatient mortality rate, one risk factor with a 1% inpatient mortality rate, two with a 3% inpatient mortality rate, three with a 9% inpatient mortality rate, four with a 15% inpatient mortality rate, and five with a 25% inpatient mortality rate.^{175,176} However, recent studies have reported limitations of AIMS65, and suggest that further validation of this scoring system is needed.^{177,178}

There are no widely used scoring systems for LGIB. However, predictors of adverse outcome and severity in LGIB include hemodynamic instability 1 hour after initial evaluation, active gross bleeding per rectum, and initial HCT \leq 35%.¹⁷⁹

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Acute Liver Failure

Cindy H. Hsu • Ashley R. Menne • Samuel A. Tisherman

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Regardless of etiology, the unifying feature of acute liver failure (ALF) is a rapid, often precipitous, clinical course. Whereas spontaneous recovery of liver function is possible with supportive measures, particularly with acetaminophen overdose, there remains a significant risk of spiraling decline after presentation with multi-organ dysfunction, bleeding, and infectious complications often heralded by high-grade encephalopathy with cerebral edema.¹ A patient who presents emergently with ALF has an overall greater likelihood of either dying or requiring emergent orthotopic liver transplantation (OLT) than recovering without transplant.²

The key message for the emergency critical care practitioner is that early management of a patient with ALF requires an orchestrated team effort to rapidly and efficiently triage and mobilize management resources. Because of the rarity and complexity of ALF, it has been argued that ALF is best managed within the framework of a previously defined protocol, similar to the standards that have gained broad acceptance in stroke and acute coronary syndrome.³ Such team efforts are crucial to give the patient with ALF the best opportunity for transplant-free survival. In the setting of deteriorating status, teams are required to rapidly mobilize those resources, interventions, and caregivers that are crucial to provide stabilization and life support as well as rapid triage for transplantation in a crisis setting when the time course may not forgive hesitation.

Recommendations and best evidence for developing this approach have been published by the Acute Liver Failure Study Group (ALFSG)⁴ and the American Association for

the Study of Liver Disease (AASLD).⁵ Both references consist of recommendations from a consortium of transplant centers that continue to prospectively collect data, report their findings, and grade the level of evidence.

This chapter is designed as a practical guide for the emergency critical care practitioner to manage ALF. An organizational framework for key clinical interventions is presented.

FIRST CONTACT: DEFINITION, RECOGNITION, AND DIAGNOSIS

Often used interchangeably, both the terms ALF and fulminant hepatic failure are defined by the new onset of hepatocellular dysfunction as reflected by coagulopathy (international normalized ratio [INR] > 1.5) and encephalopathy in the absence of preexisting liver disease.⁶ By convention, the further stratification of fulminant hepatic failure is based on the rapidity of encephalopathy onset in the course of illness: less than 2 weeks for acute fulminant and 8 weeks for subfulminant.⁷ The ALFSG consortium has extended that time course up to 26 weeks for entry into their multicenter data analysis, and have adopted the term ALF, arguing that this captures the variable pace of illness in ALF, and better encompasses an extended range of patients who share epidemiologic, etiologic, physiologic, and management characteristics.⁸ In the absence of encephalopathy or coagulopathy, population-based studies of patients at risk of ALF have defined hepatotoxicity by ALT > 1,000.⁹

How to Suspect the Diagnosis

As suggested by the variable terminology, the patient with ALF in the absence of prior liver disease may present with strikingly variable chief complaints and duration of symptoms. A common symptom complex of subacute fatigue, malaise, nausea, and mental status changes may be subtle and may not point overtly to ALF, particularly if transaminase and INR determination are not part of the initial screen. Therefore, a high level of suspicion and awareness of vague or nonspecific complaints is required for astute and rapid recognition of this disease.

Epidemiology, Etiology, and Outcomes

The emergency critical care practitioner should be aware of the common etiologic categories so as to focus attention during this key initial encounter. Globally, viral infections such as hepatitis A and E are responsible for the majority of ALF, whereas drug-induced liver injury is the predominant cause in the developed world.¹⁰ A handful of categories account for the bulk of etiologies, although the complete list of possible causes is extensive.

In North America, acetaminophen accounts for nearly half of the ALF caused by drug toxicity. Other, significantly less common, drugs include anti-tuberculous agents (particularly, isoniazid and pyrazinamide), antiepileptic drugs (particularly, valproic acid), antibiotics, and herbal supplements (Tables 24-1 and 24-2).^{5,11} Other identifiable causes of ALF include acute hepatitis B virus (HBV) infection (7%), other



TABLE 24-2: Herbal Products/Dietary Supplements Associated with Hepatotoxicity

Kava Kava	Greater celandine
Herbalife	He Shon Wu
Hydroxycut	LipoKinetix
Comfey	Ma Huang
Senecio	Poison mushrooms (<i>Amanita phalloides</i>)

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viral infections (3%), autoimmune hepatitis (5%), ischemic hepatitis (4%), and various other causes (5%) such as Wilson's disease, pregnancy-associated ALF, and other metabolic pathway abnormalities. Of importance, up to 15% of ALF cases remain of indeterminate etiology.¹¹

The first, and perhaps most essential, challenge is to make every attempt to obtain a complete and detailed ingestion history. To be sure, this should include all prescribed medication along with an accurate timeline. But of equal importance is that every attempt must be made to identify all nonprescription therapy, illicit drug use, alternative/nontraditional and herbal remedy use, and nonmedicinal ingestions (e.g., *Amanita* mushroom, nutritional or fitness supplements) that are new or noteworthy.¹² Alcohol consumption should be scrutinized, although underreporting should be objectively ascertained by blood levels.¹³ Likewise, acetaminophen overdose may be underappreciated or the result of unintentional therapeutic misadventure; the toxicity profile may be affected by sustained or coadministration.¹⁴ As such, it must be impressed upon the patient and family members to recall and report all recent therapies, including familiar household remedies that might be considered innocuous.

Etiology has a measurable effect on outcome. ALF from acetaminophen overdose, pregnancy, and hepatitis A has a more favorable outcome with transplant-free survival approaching 50%.¹⁵ Spontaneous recovery is least likely with Wilson's disease, nonacetaminophen idiosyncratic drug reactions, and indeterminate causes.¹⁶ Patients who suffer ALF due to antiepileptic drugs have a significantly higher death rate after OLT than patients who have ALF due to other drugs.¹⁷

Early identification of a causal agent may be of therapeutic importance. Although treatment pathways are largely supportive and apply generically, some therapeutics may be tailored to specific etiology and may be time sensitive.

Initial Lab Tests: Diagnosis, Prognosis, and Transplant Screens

In the context of history-taking challenges, initial laboratory studies are crucial to sift through the diagnostic questions, and to lay the groundwork for assessment of OLT candidacy. In addition to liver function testing and INR, initial screening etiologic diagnostic studies should be sent as soon as feasible.



TABLE 24-1: Drugs That May Cause Idiosyncratic Liver Injury Leading to ALF

Abacavir	Isoniazid
Acetaminophen	Itraconazole
Allopurinol	Ketoconazole
Amiodarone	Labetalol
Amoxicillin-clavulanate	Methyldopa
Carbamazepine	3,4-methylenedioxy-methamphetamine (MDMA)
Ciprofloxacin	Nicotinic acid
Cocaine	Nitrofurantoin
Dapsone	Phenytoin
Diclofenac	Propylthiouracil
Didanosine	Pyrazinamide
Disulfiram	Rifampin-Isoniazid
Doxycycline	Statins
Efavirenz	Sulfasalazine
Etodolac	Terbinafine
Gemtuzumab	Tolcapone
Imipramine	Trimethoprin-sulfamethoxazole
Isoflurane	Valproic acid

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Acetaminophen levels provide the best guidance in the setting of single ingestion history, whereas prediction of ALF by nomogram has the greatest utility if the timing of ingestion is verifiably ascertained.¹⁸ Liver failure is typically associated with single ingestion in excess of 10 g, and unlikely with less than 4 g.¹⁹ However, in the setting of polypharmacy coingestion or chronic ingestion, a far lower intermittent dosage may result in hepatocellular loss. Accordingly, the receiver operating characteristic of a single acetaminophen level may have reduced negative predictive power in these settings, thus cannot exclude acetaminophen toxicity as causal.²⁰ Assay for acetaminophen–protein adducts may be available in some centers; this sensitive assay may provide clues of unappreciated acetaminophen toxicity when ALF etiology remains indeterminate.²¹

Initial evaluation should also help to rule out mimics that may present with a similar triad of transaminitis or hyperbilirubinemia, coagulopathy, and altered mental status. When an initial exam suggests another etiology, ultrasound examination may provide clues to biliary tract obstruction, infiltrative hepatopathy, tumor, hepatic vein obstruction, or acute exacerbation of chronic liver disease. Nonprimary hepatic disease such as sepsis, hemolytic crisis, and acute pericardial constriction may confound the initial assessment if coagulation abnormalities or hyperbilirubinemia are prominent. Warfarin ingestion and consumptive coagulopathy must be considered with isolated coagulopathy. Also, adverse drug reactions may occur in the context of superimposed or concomitant illness that may further cloud the distinction between hepatocellular injury and another systemic illness.

Once the diagnosis of ALF is firmly suspected or confirmed, it is essential to obtain a battery of additional laboratory studies without delay. These studies are designed to discriminate among principal ALF etiologies, further characterize the extent of hepatocellular injury, screen for metabolic derangement, and elicit nonhepatic issues that may need attention or may impact OLT candidacy. Table 24-3 provides a comprehensive list of laboratory tests that are indicated. Given the magnitude and complexity of this large list, a pre-established order set that is triggered by protocol is highly recommended.

Prognosticating from First Contact

Establishing a clear baseline, based upon history, physical exam findings, and initial laboratory findings, for serial comparison and ALF trajectory is critical for risk stratification and subsequent decision-making, particularly whether or not to list a patient for transplantation. The most commonly used prognostic classification scheme, the King's College Hospital criteria (Table 24-4), uses simple measures that negatively predict transplant-free survival, originally derived from a cohort of patients with acetaminophen-induced ALF.²² An unambiguous baseline and a standardized plan to serially obtain and clearly document these specific components should be part of the emergency critical care team plan.

Data that support the additive value of additional serum markers of poor outcome have been debated among



TABLE 24-3: Immediate Laboratory Screen on Suspicion of ALF

Document hepatocellular injury and initiate systemic/etiologic inquiry	Liver function panel Ammonia level Amylase and lipase PT/INR Complete blood count with differential Fibrinogen Acetaminophen level (adduct if available) Toxicology screen Electrolytes/creatinine/uric acid Blood cultures Pregnancy test (if female)
Etiology evaluation	Cytomegalovirus IgG Epstein–Barr virus IgG Hepatitis A virus IgM Hepatitis B virus DNA (quantitative) Hepatitis B surface antigen Hepatitis B surface antibody Hepatitis B core antibody Hepatitis C virus RNA (quantitative) Hepatitis C antibody Herpes simplex virus IgM Varicella zoster virus α -Fetoprotein Ceruleplasmin Serum protein electrophoresis α -Smooth muscle antibody Antimitochondrial antibody Antinuclear antibody Liver kidney microsome antibody
Severity of hepatic and extrahepatic disturbance, and transplant triage	HIV-1, HIV-2 Urinalysis Arterial blood gas Arterial lactate ABO (two separate tests, 2 hours apart) Repeat PT/INR every 6 hours Repeat transaminase level every 6 hours Repeat total and direct bilirubin every 6 hours

the transplant community.^{23–25} Likewise, disease-specific prognostic indices have been evaluated in relatively small cohorts that require further validation.²⁶ To date, the King's College Hospital criteria remain the most clinically useful, with a sensitivity of 68% to 69% and a specificity of 82% to 92%.²⁷ Newer prognosticative tools such as the model of end-stage liver disease (MELD) was not better than the King's College Hospital criteria or INR.²⁸ Overall, the predictive value of any modality may be influenced by the interruption of the natural history of disease by transplant itself. The decision, timing, availability, and effectiveness of OLT in any given case and in different settings compound



TABLE 24-4: Predictors of Increased Mortality without Emergent Transplant: King's College Criteria

In acetaminophen-induced ALF

- Prothrombin time (PT) > 100 s (INR > 6.5)
- Arterial pH < 7.30
- Grade III or IV encephalopathy
- Serum creatinine > 300 mcg/mL (3.4 mg/dL)

In nonacetaminophen-induced ALF

- PT > 100 s
- Or three of the following five criteria:
 - Patient age < 10 or > 40 years
 - Hepatitis due to non-A/non-B virus, halothane, or drug reaction
 - Delayed onset of encephalopathy (> 1 week after onset of jaundice)
 - PT > 50 s (INR > 3.5)
 - Serum total bilirubin > 17.5 mg/dL (300 mmol/L)

Data from O'Grady JG, Alexander GJ, Hayllar KM, et al: Early indicators of prognosis in fulminant hepatic failure, *Gastroenterology* 1989 Aug;97(2):439–445.

the difficulty of comparative predictive models. Table 24-5 highlights some indicators of poor prognosis in patients with ALF who may benefit from an OLT. It is worth noting, however, that none of the factors listed (with exception of Wilson's disease and possibly mushroom poisoning) are either necessary or sufficient to indicate the need for immediate OLT.⁵

SUPPORTIVE THERAPY

How to Manage Hemodynamic Support

With progressive decline in liver function, a hyperdynamic state with low systemic vascular resistance may predominate the clinical picture, and be clinically indistinguishable from severe sepsis. This feature correlates with the Sequential Organ Failure Assessment (SOFA) score, arterial lactate, and mortality.²⁹ It is imperative to maintain the mean arterial pressure (MAP) above 75 mm Hg and the cerebral perfusion pressure (CPP) above 60 mm Hg (if intracranial pressure [ICP] monitoring is employed) to preserve renal and brain perfusion.³⁰ Volume resuscitation with 20 to 25 mL/kg isotonic crystalloid is an appropriate first maneuver. If the patient is not responsive to an initial fluid challenge, nor-epinephrine is recommended.⁴ Although earlier studies suggested that vasopressin could lead to elevated ICP, more recent data demonstrated that vasopressin and its analogs increase cerebral perfusion without increasing ICP. As such, vasopressin may be administered for patients who remain hypotensive despite adequate volume resuscitation and nor-epinephrine infusion.^{31,32}

Adrenal hyporesponsiveness is common in ALF. Corticosteroid replacement, though controversial, may be prudent and is recommended by the ALFSG for patients with refractory hypotension.⁴ Capillary permeability disturbance



TABLE 24-5: Potential Indicators of Poor Prognosis in Patients with ALF

Etiology

- Idiosyncratic drug injury
- Acute hepatitis B (and other nonhepatitis A viral infections)
- Autoimmune hepatitis
- Mushroom poisoning
- Wilson disease
- Budd–Chiari syndrome
- Indeterminate cause

Coma Grade on Admission

- Grade III or IV hepatic encephalopathy

King's College Criteria

- Acetaminophen-induced ALF
 - Strongly consider OLT listing if:
 - Arterial lactate > 3.5 mmol/L after early fluid resuscitation
 - List for OLT if:
 - pH < 7.3 or
 - Arterial lactate > 3.0 mmol/L after early fluid resuscitation
 - List for OLT if all 3 occur within a 24-hour period:
 - Presence of grade III or IV hepatic encephalopathy
 - INR > 6.5
 - Creatinine > 3.4 mg/dL
- Nonacetaminophen-induced ALF
 - List for OLT if:
 - INR ≥ 6.5 and encephalopathy present (irrespective of grade)
 - List for OLT if any 3 of the following:
 - Age < 10 or > 40 years
 - Jaundice for > 7 days before development of encephalopathy
 - INR ≥ 3.5
 - Serum bilirubin ≥ 17 mg/dL
 - Unfavorable etiology

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precipitates an increase in extravascular lung water with minimal hydrostatic pressure elevation, particularly in patients with cerebral edema, leading to a picture of the acute respiratory distress syndrome (ARDS).³³ Echocardiography is indicated to help titrate hemodynamic support and to exclude superimposed cardiac contractile dysfunction, pericardial disease, or undisclosed regional wall motion abnormality that may impact surgical and anesthesia tolerance. Serum troponin elevation is prevalent in ALF with shock, as in other forms of critical illness, and may portend a poor prognosis.⁴

When to Initiate Empirical Antibiotics

With an increased duration and severity of liver dysfunction, the incidence of systemic infection rises, stemming from a blunted innate immune response coupled with catheter- and ventilator-associated barrier disruption.⁴ Both bacterial and fungal pathogens have been reported. Periodic surveillance

cultures are recommended to detect these pathogens as early as possible.⁵ The presence of a systemic inflammatory response syndrome and refractory hypotension with progression to advanced-stage hepatic encephalopathy in the patients listed for OLT often warrants empirical antibiotics.⁴ However, empirical antibiotic and antifungal administration have not been shown to improve overall survival in ALF, therefore cannot be advocated in all patients, especially those with mild hepatic encephalopathy.⁵

Management of Bleeding and Bleeding Risk

Patients in ALF can present with abnormalities at multiple levels of the coagulation cascade. Aside from coagulation factor and fibrinogen deficiency due to synthesis disorders, patients may present with thrombocytopenia due to splenic sequestration, disseminated intravascular coagulation (DIC), or platelet abnormalities because of uremia and acute renal insufficiency. However, a recent study suggested that overall hemostasis as measured by thromboelastography is normal even in patients with markedly elevated INR.³⁴ Injudicious use of plasma components can obscure the triage assessment for transplantation by artificially decreasing INR. These products can also increase the risk for gas exchange disturbance due to hydrostatic pulmonary edema.⁴ Furthermore, clinically significant bleeding in ALF patients is rare.³⁵ Thus, prophylactic infusion of plasma or platelets is not recommended except for clinically significant bleeding or anticipation of a high-risk procedure.⁵

It has been recommended that the use of recombinant factor VIIa (rFVIIa) be restricted to coagulopathy reversal only in the setting of severe volume overload with predicted FFP intolerance, or prior to high-risk procedures such as liver biopsy or ICP monitor placement. The use of rFVIIa does not replenish other depleted coagulation factors and carries a higher risk of DIC than other agents.³⁶ Additionally, the rate of arterial thrombotic events with rFVIIa is as high as 8.5%.³⁷

Unactivated prothrombin complex concentrates (PCCs) are marketed as Bebulin and Profilnine in the United States and Octaplex in Europe, and are sometimes referred to as factor IX concentrates. Kcentra is the first four-factor PCC to be approved in the United States. These products include varying amounts of factors II, VII, IX, X and proteins C and S. Using PCCs, coagulopathy reversal of multiple factors can be achieved quickly with minimal volume and at a lower expense than rFVIIa. Since PCCs do not contain factor V, some hematologists recommend additional FFP to replace this factor. All patients should receive vitamin K 10 mg intravenous (IV).⁵ In addition, if the fibrinogen level is below 100 mg/dL, administration of cryoprecipitate may be indicated. Patients who have renal insufficiency should receive desmopressin (DDAVP) 0.3 mcg/kg once for uremia-induced platelet dysfunction.

Adequate laboratory values for the placement of an ICP monitor include INR < 1.5, platelets > 50,000/mm³, fibrinogen > 100 mg/dL, and a normal PTT. It should be noted that multiple doses of rFVIIa or the combination of rFVIIa

and PCCs are not recommended as this can dramatically increase the risk of DIC and DIC-related complications. In patients with persistent coagulopathy, plasma exchange has been shown to be effective.⁴ This may be an especially attractive option in patients who already have a dialysis catheter in place and who can tolerate an interruption from renal replacement therapy to undergo plasma exchange.

Central Line Timing and Safety Issues with Placement

In patients with severe encephalopathy, it is most prudent to combine the acts of sedation, intubation, central line access, and blood product support, followed by an assessment for transport to obtain head and abdominal computed tomography (CT). Concern for enhanced risk of catheter-associated bloodstream infection limits the utility of femoral vein cannulation. An internal jugular (IJ) approach is preferred over the subclavian because of improved ultrasound visualization and the ability to compress the vessel if bleeding occurs. There are no contraindications to IJ line placement in patients with an elevated ICP, although maintaining the head in neutral position and avoiding bilateral IJ cannulation is preferred.

Electrolyte and Fluid Management

Hypoglycemia is common and needs to be expectantly screened for and managed with glucose-containing solutions as hepatic function deteriorates. To avoid excess free water administration, glucose should be administered as 10% solution. Metabolic acidosis often complicates ALF, with decreased lactate flux, increased lactate production, and increased strong ion gap values that maintain a persistent base deficit despite the alkalinizing effects of hypoalbuminemia and hyponatremia.³⁸ Likewise, citrate-, acetate-, and gluconate-containing solutions may be poorly handled by the failing liver, and may represent an additional burden of unmeasured anions that can contribute to a strong ion difference and unmitigated acidosis.³⁹

Multiple aspects of ALF tend to produce hyponatremia. A deleterious effect of poorly managed water balance on patient outcomes has been observed, with both worsening encephalopathy and a significant decline in posttransplant neurologic recovery in recipients who had serum sodium < 130 mEq/L at the time of surgery.⁴⁰ Phosphate, magnesium, and potassium levels are frequently low and may require frequent repletion. Interestingly, hypophosphatemia is a notable exception to the deleterious effect of electrolyte disturbance, in that it has been attributed to recovering hepatocyte mass and is considered to be a marker of renewed metabolic activity.⁴ Enteral feedings should be initiated early whenever possible to reduce stress-related mucosal disease, maintain gut integrity, and possibly decrease the risk of nosocomial infections. If enteral feeding is contraindicated, parenteral nutrition should be considered.⁵ Gastrointestinal prophylaxis with either a proton pump inhibitor or histamine receptor 2 antagonist is standard at most centers and should be promptly initiated.

When to Initiate Renal Replacement Therapy

Oliguria and acute kidney injury are common complications of ALF. The predilection for renal failure is highest in acetaminophen toxicity or other hepatotoxins with direct nephrotoxicity (e.g., *Amanita* poisoning or trimethoprim-sulfamethoxazole), but may be precipitated in all forms of ALF.^{18,41} The pathogenesis is likely multifactorial and may include hypovolemia, acute medullary cortical microcirculatory disturbance with a prerenal picture similar to hepatorenal syndrome, or tubular damage directly from toxins, including acetaminophen adducts or associated reactive oxygen species.⁴² Considerable efforts should be made to minimize renal injury by maintaining adequate perfusion, avoiding nephrotoxic drugs such as aminoglycosides and nonsteroidal anti-inflammatory drugs (NSAIDs), and treating infections promptly.⁵ The recovery of renal function tends to mirror that of hepatic function, so that spontaneous improvement with recovery or improvement after transplantation are often seen. Nonetheless, early introduction of renal replacement therapy is recommended for patients with progressive oliguria, particularly in the setting of electrolyte disturbances and volume overload, to assist the management of plasma administration or osmotic therapies.⁴ Continuous venovenous hemofiltration (CVVH) is the preferred modality because it causes less fluid shifts and hemodynamic compromise. Plus, it can be used to rapidly and continuously address electrolyte disturbances and manage osmotic therapy.^{4,5}

Specific Therapeutic Initiatives

The toxic acetaminophen metabolite *N*-acetyl-*p*-benzoquinone imine (NAPQI) is normally detoxified by glutathione conjugation. In acetaminophen overdose, the hepatic glutathione supply is depleted, thereby leading to the accumulation of toxic NAPQI and subsequent ALF. *N*-acetylcysteine (NAC) can be administered via oral or intravenous (IV) route to replenish glutathione, and may further act by antioxidant and vasoactive mechanisms. The IV route has the advantage of eliminating concerns related to gut absorption when gastrointestinal function is compromised.⁴ Moreover, based on accumulating evidence for transplant-free survival benefit and its generally favorable safety profile, IV NAC should be strongly considered for patients with early-stage nonacetaminophen ALF.⁴³ Treatment should be initiated immediately when ALF or hepatotoxicity is established, with a loading dose of 150 mg/kg in 500 mL dextrose 5% over 30 minutes, followed by maintenance dose 50 mg/kg over 4 hours, then 125 mg/kg in 1,000 mL dextrose 5% over 19 hours. Although NAC should be administered as early as possible, it may still be of value 48 hours or more after ingestion.⁴⁴ Most experts recommend a continuous IV infusion of NAC until the INR is less than 1.5. Because of risk of hypersensitivity reaction, IV NAC should always be administered in a monitored setting. Patients with mild allergic symptoms should have the infusion rate decreased by 50% and receive corticosteroids and antihistamine.

Other therapies in use, but of unproven benefit, include activated charcoal and high-dose IV penicillin G for mushroom poisoning, and corticosteroids for autoimmune hepatitis. However, corticosteroids had no demonstrated benefit in a trial of drug-induced ALF. Other emergent interventions that apply to specific etiologies include prompt delivery for pregnancy-related ALF. Consultation with the transplantation team should be conducted before the initiation of etiology-specific therapy with unproven initiatives such as copper chelation, plasmapheresis, and antioxidant therapy for Wilson's disease; lamivudine or entecavir for acute hepatitis B; acyclovir for herpes simplex virus infection; and decompressive surgery or transjugular intrahepatic portosystemic shunts (TIPS) for acute Budd–Chiari syndrome.¹¹

Emerging Therapeutic Options in ALF

Hemofiltration and hemodialysis have limited capacity to remove protein-bound toxins, but newer experimental techniques have been developed to deal with these substances. Several configurations of so-called liver support modalities have been reported in nonrandomized studies, and the results of multicenter trials are pending. Both cell-free and bioartificial systems have been developed with the aim to remove known and unknown toxins that are released and not cleared in ALF. At present, the use of these devices has not been reported to change mortality, although endpoints such as reduced encephalopathy have raised interest in pursuing this line of research. However, their use should be considered experimental.⁴⁵

Bridging therapies such as auxiliary orthotopic transplant and two-stage transplantation, in which hepatectomy precedes transplantation by a variable interval up to days, are controversial and have only been reported anecdotally. These extraordinary procedures are attempted only in specialized centers under dire circumstances, as in the setting of unavailable allograft in a patient with unmitigated intracranial hypertension.⁴⁶

ORCHESTRATING THE RESPONSE TO WORSENING ENCEPHALOPATHY

How to Evaluate Mental Status

Hepatic encephalopathy is a reversible form of neurologic dysfunction. Although its pathogenesis is not entirely understood, it is thought to be primarily due to ammonia-induced neurotoxicity. Ammonia, produced either by catabolism of nitrogenous sources or by glutamine metabolism at a mitochondrial level, has been shown to lead to astrocyte swelling and dysfunction.⁴⁷ Metabolism of glutamine into glutamate and ammonia may also cause stimulation of *N*-methyl-D-aspartic acid (NMDA) receptors triggering nitric oxide release and subsequent vasodilation. This vasodilation may lead to hyperemia and cerebral edema.⁴⁸ Additionally, cerebral autoregulation is impaired in patients with fulminant hepatic failure.⁴⁹ A variety of other mechanisms may be involved in the pathogenesis of hepatic encephalopathy, including

inflammation, activation of the aquaporin-4 water channel protein on astrocytes, oxindole (a tryptophan metabolite), as well as catecholamine and other neurotransmitter abnormalities.⁵⁰ The result of this abnormal neurochemical milieu is cerebral edema, which occurs in 80% of comatose patients and is the leading cause of death among patients suffering from fulminant ALF.⁵¹ Hepatic encephalopathy grades are depicted in Table 24-6.

The neurologic exam should be conducted in patients who have been free of sedation for as long as possible, balancing the risks of agitation that may elevate ICP. Since neuromuscular blockade can alter brainstem reflexes and the motor exam, recently intubated patients should be tested with train-of-four stimulations to ensure that neuromuscular blockade is not confounding the neurologic assessment. Table 24-7 outlines the neurologic domains that should be assessed in all patients with ALF.

When to Obtain Head CT Scan

Any patient with an acute deterioration in mental status or focal findings on exam should undergo a noncontrast head CT to assess for intracranial hemorrhage. Apart from this, a head CT is recommended in any patient with stage III or IV encephalopathy to evaluate for cerebral edema.⁴ A normal head CT does not rule out elevated ICP and should not be used as a surrogate for ICP monitoring. In addition to a baseline CT, a repeat head CT should be performed after the insertion or removal of an ICP monitor to check positioning and for hemorrhage. Although magnetic resonance imaging (MRI) may detect cerebral edema with more sensitivity and specificity than CT, the risks of transport and the time involved in obtaining an MRI outweigh the benefits in diagnostic accuracy.

When and How to Intubate

Encephalopathy can lead to aspiration and elevated Paco_2 , which can exacerbate cerebral edema and elevated ICP. Practitioners should consider intubating patients who cannot follow commands (typically with hepatic encephalopathy grade III or IV). In order to avoid spikes in ICP that can occur with laryngeal stimulation, intubation should occur in a controlled setting. Either propofol or etomidate is an appropriate induction agent. Ketamine should be avoided because of its potential to elevate ICP, although this is controversial. Lidocaine spray or 1 mL/kg IV bolus can be given prior to laryngoscopy to blunt increases in ICP. The use of a video-assisted laryngoscope can facilitate first-attempt success with intubation.

Safe Mechanical Ventilation and Principles of ICP Interaction

Assist control or volume control modes are reasonable in patients with hepatic encephalopathy. Since increasing positive end-expiratory pressure (PEEP) will increase mean intrathoracic pressure as well, elevated PEEP that exceeds central venous pressure can theoretically lead to elevations in ICP. However, studies with PEEP up to 15 cm H_2O have not shown a significant effect on ICP or CPP.⁵² Inverse ratio modes of ventilation with elevated pressures for a significant duration of the respiratory cycle may inhibit jugular venous outflow and lead to increased ICP. Permissive hypercapnia should be avoided as this will elevate ICP. Many patients with ALF will spontaneously hyperventilate as part of an autoregulatory response, which should not be suppressed. Conversely, induced hyperventilation is not recommended except in acute cases of herniation since this can lead to ischemia due to vasoconstriction.⁵³ Maintenance of a Paco_2 between 30 and 40 mm Hg is reasonable.



TABLE 24-6: Hepatic Encephalopathy Grade

Grade	Level of Consciousness/ Cognitive Function	Neuromuscular Function	Psychiatric Symptoms
I	Sleep disturbance Mild confusion Impaired computations	Tremor Incoordination \pm Asterixis	Euphoria/depression
II	Inattentive Moderate confusion Disorientation to time	Asterixis Slurred speech Impaired handwriting	Irritability Decreased inhibitions Personality changes
III	Marked confusion Completely disoriented Lethargic, but arousable Command following	Slurred speech Ataxia Asterixis Nystagmus Hypoactive or hyperactive reflexes	Anxiety or apathy Inappropriate or bizarre behavior Paranoia, anger, or rage
IV	Noncommand following coma	Dilated pupils Loss of cranial nerve reflexes Signs of herniation Flexor or extensor posturing Loss of reflexes	Coma



TABLE 24-7: Neurologic Assessment of the Patient with ALF

Neurologic Domain	Exam Features	Alarming Findings
Mental status	Orientation to self, place, time Level of attentiveness (backwards counting or months) Evaluate language (command following, fluency, naming, repeating) Evaluate higher-level cognitive functioning (calculation, praxis) Evaluate for mood disturbance	No command following Does not open eyes to voice or tactile/noxious stimulation No verbal output Does not track or saccade to voice Any change in level of attentiveness should trigger a more aggressive neurologic evaluation
Cranial nerves	Pupil reactivity, diameter, symmetry Fundoscopy to assess for papilledema, retinal hemorrhages Oculocephalic reflex (doll's eyes) Corneal reactivity (tests CN V afferent, VII efferent) Trigeminal sensation Facial symmetry Gag, palate elevation Tongue deviation	Dysarthria may indicate facial weakness or cerebellar dysfunction Loss of brainstem reflexes is an ominous sign Asymmetric pupil dilatation may indicate herniation
Motor exam	Assess upper- and lower-extremity motor strength. Pronator drift may be an early sign of focal abnormality. Noxious stimuli may be necessary to assess for posturing in grade III and IV patients. Assess for asterixis by having patient hold out hands as though the patient is "stopping traffic." Asterixis is negative myoclonus or loss of muscle tone and can prompt falls if lower-extremity asterixis is present.	Any new focal deficit should raise concern for intracranial hemorrhage. Flexor or extensor posturing occurs in grade IV encephalopathy.
Sensory exam	Test to modalities of light touch, pinprick, pain, temperature, vibration, and proprioception.	The sensory exam is notoriously unreliable in encephalopathic or inattentive patients.
Cerebellar exam	Appendicular function: finger to nose, heel to shin Axial function: titubation, dysarthria, ataxia	Cerebellar dysfunction occurs early in hepatic encephalopathy.
Gait	Evaluate normal gait, toe and heel walking and tandem gait, Romberg testing	Wide-based gait and an inability to place feet together or in tandem indicate cerebellar dysfunction.
Reflexes	Deep tendon reflexes are graded as absent, 1+ (diminished), 2+ (normal), 3+ (hyperactive with spread but no clonus), 4+ (hyperactive with clonus) Babinski	Hyperactive or hypoactive reflexes can occur. Upgoing toes occur with higher-grade encephalopathy.

Sedation Practices in the Face of Encephalopathy

Minimizing oversedation and utilizing sedation interruption are essential for continuous assessment of the neurologic exam. On the other hand, adequate treatment of pain and anxiety should be addressed to minimize elevation of ICP. When selecting a sedative, renal and hepatic clearance should similarly be considered. Propofol is a typical agent with a short half-life that allows for frequent exam assessment. It does not provide any analgesia, however. Other reasonable options include fentanyl, which can minimally lower the seizure threshold, and dexmedetomidine, a centrally acting α_2 -agonist that provides anxiolysis and analgesia with minimal respiratory or neurologic suppression. Midazolam is a reasonable choice in anxious patients and, like propofol, has anticonvulsant effects. It does, however, have active metabolites that can accumulate with prolonged use. All of the aforementioned agents can lower blood pressure. Neuromuscular

blockade is seldom necessary for adequate ventilation, but, if required, it should be used judiciously and for as brief a period of time as necessary. It can substantially increase the risk for critical illness neuropathy and myopathy, mask seizure activity, and completely obscure the neurologic exam.

Lactulose

There is increasing evidence that ammonia plays an important role in the pathogenesis of not only encephalopathy, but also cerebral edema. In ALF, the speed of development of hyperammonemia renders the usual osmotic compensatory mechanisms ineffective, unlike subacute or chronic liver failure, in which intracranial hypertension is not common. A detailed analysis of serum ammonia in patients with ALF identified a concentration of 75 μM as an important threshold below which patients rarely develop intracranial hypertension.⁵⁴ Conversely, a serum ammonia level of $> 100 \mu\text{M}$ on admission represents an independent risk factor for the

development of high-grade hepatic encephalopathy, and a level of $> 200 \mu\text{M}$ is strongly associated with cerebral herniation.⁵⁵ A retrospective study conducted by the ALFSG showed a small increase in survival time of those who received lactulose, but no difference in the severity of encephalopathy or overall outcome.⁵⁶ As such, the AASLD recommended that oral or rectal lactulose may be administered in the early stages of encephalopathy, but should not induce diarrhea as that may interfere with OLT by causing bowel distention.⁵

ICP Monitor

Elevated ICP occurs in 86% to 95% of patients with grade III or IV encephalopathy.³ Given the insensitivity of head CT to assess for cerebral edema, ICP monitoring should be considering in all patients who do not follow commands, typically grade III or IV encephalopathy patients. Monitoring ICP is the only way to diagnose elevated ICP and assess the efficacy of cerebral edema treatment in patients with marginal neurologic exams. ICP monitors also enable the assessment of the CPP, which is calculated as MAP minus ICP. The goal in management of intracranial hypertension is to lower ICP to $< 20 \text{ mm Hg}$ while maintaining CPP of $> 60 \text{ mm Hg}$.⁵ Although there are no randomized trials to support the use of ICP monitoring, data suggest that monitoring can identify ICP spikes that are subclinical, lead to therapeutic changes, and provide important prognostic information. ICP monitoring is recommended by the ALFSG in grade III and IV patients who are candidates for transplantation and in some patients with advanced encephalopathy who are not liver transplant candidates, but may have survival benefit with protocolized, aggressive management aimed at preventing or treating intracranial hypertension.³

Since it is not clear that the risk of hemorrhage after adequate correction of coagulopathy is higher with intraparenchymal compared with epidural ICP monitors, the placement of intraparenchymal monitors is preferable due to their better accuracy. Intraventricular monitor placement is not recommended due to the increased risk of bleeding.⁵⁷

In patients who are unable to undergo ICP monitor placement, transcranial Doppler assessment of pulsatility index (peak end-diastolic flow velocity/mean flow velocity) can provide a rough assessment of ICP elevation, but cannot quantify the ICP. Pulsatility indices > 1.5 are considered abnormal. It is important to note that transcranial Doppler does not provide quantifiable or continuous ICP monitoring. Some studies have demonstrated suboptimal sensitivity and specificity.⁵⁸

Adequate reversal of coagulopathy is essential prior to ICP monitor placement. It is unclear if coagulation factors need to be corrected for the entire time an ICP monitor is in place or if correction is only necessary during placement and removal of devices.³ Continued aggressive coagulopathy correction can lead to volume overload, thrombosis, or DIC, and may mask spontaneous liver recovery. The expense of continued correction should also be considered.

Active Management—Principles of Osmotic Therapy, Hypothermia

The first steps in managing elevated ICP (defined as sustained ICP $> 25 \text{ cm H}_2\text{O}$ or 20 mm Hg) involve simple measures to maximize venous outflow and avoid increases in intrathoracic or intra-abdominal pressure that can occur with agitation, coughing, or ventilator dyssynchrony. All patients should have the head of the bed elevated at least 30° (unless contraindicated by hypotension). In addition, the head should be maintained midline to promote venous drainage, bilateral jugular venous catheterization should be avoided, and the patients should be maintained in a comfortable pain-free state with the minimal amount of analgesics or anxiolytics required to avoid agitation or pain. Lidocaine spray can be used prior to suctioning to avoid a cough response, and an adequate bowel regimen should be prescribed to avoid straining during defecation. Generally, patients should be maintained in a eutermic, euvoletic state.

Patients should be monitored for seizures and treated appropriately since this can elevate ICP. The true incidence of seizure in patients with ALF is not clear. In a small series of patients with ALF, seizure activity, including nonconvulsive status epilepticus, was identified in up to 32% of patients.⁵⁹ In addition, paralysis should be avoided, if possible, to allow for detection of subtle clinical seizure activity. Patients who have seized should receive antiepileptic treatment. Prophylaxis can be considered for those who have intracranial hemorrhage or very severe cerebral edema, in whom a seizure might cause herniation due to elevated ICP.⁶⁰

Since cerebral autoregulation is impaired in patients with ALF, it is important to recognize the relationship between ICP and MAP. In patients with a global loss of autoregulation, cerebral blood flow (CBF) and cerebral blood volume (CBV) will vary passively with MAP. Since CBV is one component of intracranial volume, increases in CBV may increase ICP. Thus, MAP should not be excessively high. However, if autoregulation is partially or regionally intact, small cerebral arterioles will dilate in an attempt to maintain CBF when MAP is low. When these arterioles dilate, CBV increases, possibly increasing ICP. The CPP level at which this occurs is called the vasodilatory cascade zone. Below this level of CPP, these vessels tend to collapse. Thus, at very high and very low MAPs, ICP may be elevated. For this reason, a CPP of 60 to 80 mm Hg is recommended.^{5,30}

In patients with persistently elevated ICP, osmotic therapy can be considered. Maintenance of a hyperosmotic state can be achieved with either mannitol boluses or hypertonic saline as a bolus or continuous infusion. Mannitol (20%, 1.0 g/kg or 100 g IV bolus) is a traditional agent that can be used for induction of a hyperosmotic state. It will cause diuresis and may cause hypotension and renal insufficiency. Mannitol is typically administered every 6 hours for elevated ICP or serum osmolality less than 320 mOsm/L or osmolal gap greater than 50 mOsm/kg.³ Renal insufficiency due to mannitol is typically seen with doses above 200 g per 24 hours or with a serum osmolal gap above 60 to 75 mOsm/kg.

Alternatively, hypertonic saline (300 mL of 3% over 10–20 minutes via a central line, then 1 mg/kg/h infusion if necessary) may be used. Hypertonic saline will improve CPP to a greater extent than mannitol, but can cause flash pulmonary edema or hypotension if administered too quickly. For highest-risk patients (serum ammonia > 150 μ M, grade III/IV hepatic encephalopathy, acute renal failure, vasopressor requirement to maintain adequate MAP), it is recommended that prophylactic induction of hypernatremia to a serum sodium of 145 to 155 mEq/L be achieved to prevent cerebral edema.^{5,61} Serum sodium values should be evaluated at least every 6 hours, and the infusion rate should be titrated accordingly. Although hypertonic saline can also cause renal insufficiency, the risk is less than that with mannitol. Both mannitol and hypertonic saline have rheologic effects that can improve ICP. Care should be taken to avoid abrupt withdrawal of hyperosmolar treatment, as this can lead to rebound cerebral edema.

Patients who are refractory to maximal osmolar therapy should be considered for induced hypothermia targeted to a core body temperature of 32 to 34°C, although it has not been studied in large randomized trials and may be associated with potential complications, such as increased risk of infection, coagulopathy, and cardiac arrhythmia.^{62,63} Other options for ICP control include hyperventilation and barbiturate coma. Hyperventilation to P_{aCO_2} of 25 to 30 mm Hg restores cerebrovascular autoregulation, resulting in vasoconstriction and reduction of ICP.⁶⁴ However, vasoconstriction can cause significant ischemia and the effect of hyperventilation is short lived (< 24 hours) since the cerebral spinal fluid (CSF) will rapidly buffer the alkalotic effect. Thus, hyperventilation should only be used acutely during herniation. Barbiturate coma is considered the last course of action for ICP control in liver failure patients. Pentobarbital (5–20 mg/kg IV bolus followed by 1–4 mg/kg/h) is typically used and titrated to burst suppression on continuous electroencephalography (EEG). Barbiturates cause loss of the entire neurologic exam, including brainstem reflexes, and carry the complications of cardiosuppression, profound hypotension, and immunosuppression. However, barbiturates can be effective in lowering ICP when patients are refractory to all other agents.

HOW TO PUT IT ALL TOGETHER: TRIAGE, TEAMWORK, TRANSPLANT CANDIDACY, AND EFFICIENT TRANSFER OF DATA

Clearly, an organized protocol with emergency department participation is required for the efficient care of ALF patients. The emergency critical care practitioner is most often the first provider to evaluate the patient and is best situated in the clinical arena to initiate the triage, diagnosis, and teamwork for this complex, though thankfully, rare condition. Most, if not all, transplant centers have developed and implemented protocolized care with predetermined order sets and identified personnel who respond to triage triggers. Components

of an organized protocol should include laboratory studies, specific consultations, and supplementary studies that are always indicated. Also, triggers for specific therapeutic interventions such as encephalopathy management should be developed with the consultants. For the best practice in a given location, the emergency critical care responder must coordinate with the local transplant center to predetermine what information will be required by the transplant team.



TABLE 24-8: Intensive Care of ALF

Cerebral Edema/Intracranial Hypertension

Grade I/II Encephalopathy

- Consider transfer to liver transplant facility and listing for transplantation
- Consider NAC
- Head CT to rule out other causes of altered mental status
- Avoid stimulation
- Avoid sedation
- Lactulose may be helpful

Grade III/IV Encephalopathy

- Continue management listed above
- Intubation
- Elevate head of bed
- Maintain CPP > 60 mm Hg
- Consider placement of ICP monitoring device
- Immediate treatment of seizures
- Mannitol: use for severe elevation of ICP or first clinical signs of herniation
- Hypertonic saline: raise serum sodium to 145–155 mEq/L
- Hyperventilation: effects short-lived; may use for impending herniation

Infection

- Surveillance for and prompt antimicrobial treatment of infection
- Antibiotics prophylaxis possibly helpful but not proven

Coagulopathy

- Vitamin K: give at least one dose
- FFP: give only for invasive procedures or active bleeding
- Platelets: give only for invasive procedures or active bleeding
- Recombinant activated factor VII: possibly effective for invasive procedures
- Prophylaxis for stress ulceration with histamine 2 blocker or proton pump inhibitor

Hemodynamics/Renal Failure

- Volume replacement
- Pressor support to maintain MAP > 75 mm Hg; vasopressin may be used in hypotension refractory to volume resuscitation and norepinephrine
- Avoid nephrotoxic agents
- Continuous modes of hemodialysis if needed

Metabolic Derangements

- Monitor glucose, potassium, magnesium, and phosphate closely
- Nutrition: enteral feedings if possible or total parenteral nutrition

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Finally, if the diagnosis of ALF appears likely or is confirmed, the emergency critical care practitioner should be mindful of the specific demographic information that would be required of a transplant coordinator should the need arise to list the patient with the United Network of Organ Sharing (UNOS) waiting list. Ensuring the completeness of these historical components at the time of presentation may be critical to the prevention of transplant delay and is best accomplished by a prescribed protocol. Table 24-8 highlights the critical steps in the acute management of ALF and can be adapted to assist in the care coordination for patients with this complex disease.

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Chronic Liver Failure

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Chronic liver failure involves virtually every major organ system. Emergency management can be complicated and is characterized by recognition of the many complications.

The management of chronic liver failure is distinct from acute liver failure. While the management of acute liver failure is directed toward preventing early death, addressing reversible causes, and coordinating transplant, the management of chronic liver failure is centered around recognizing and managing complications. This chapter will review the most common of these complications in a system-based fashion.

EPIDEMIOLOGY, ETIOLOGY, AND OUTCOMES

The etiology of chronic liver failure differs from acute liver failure. Whereas acetaminophen, medications, viral infections, and ischemia account for the vast majority of acute liver failure cases, most cases (50%–65%) of chronic liver failure can be attributed to alcohol abuse and hepatitis C. Hepatitis B accounts for an additional 10% to 15% of cases. Although miscellaneous causes such as autoimmune hepatitis, primary biliary cirrhosis, primary sclerosing cholangitis, Wilson disease, and hemochromatosis account for only 5% of all cases, these may be more commonly represented in

referral centers. Approximately 1 in 5 cases of cirrhosis are labeled as cryptogenic, although a majority of these are likely due to nonalcoholic fatty liver disease, a condition becoming increasingly prevalent in the United States, affecting 10% to 24% of the general population.¹

Regardless of the cause, progression to cirrhosis, defined as diffuse hepatic fibrosis with conversion of normal liver architecture into structurally abnormal nodules, is associated with high mortality, estimated to be as high as 50%^{2,3} while awaiting transplant, and is nearly universally fatal without transplant. Chronic liver failure is responsible for 35,000 deaths per year in the United States.⁴

MENTAL STATUS CHANGES IN LIVER FAILURE

How to Evaluate Mental Status

Mental status changes can be a frequent cause for emergency department (ED) presentation and can be one of the most distressing complications from the perspective of patients and families. The most common cause is hepatic encephalopathy, caused by a combination of astrocyte swelling and cerebral edema due to the synergistic effects of excess ammonia and inflammation.⁵ As opposed to acute liver failure, elevated

intracranial pressure (ICP) in chronic liver failure is much less common, reported at the case report level,^{6,7} and ICP monitoring rarely plays a role unless the etiology remains in question.

Evaluation should involve ruling out other potential etiologies of altered mental status while simultaneously investigating for potential precipitants. Hepatic encephalopathy is rarely attributed solely to worsening liver function due to natural history of this disease. Common precipitants are infection and lactulose noncompliance, but also include gastrointestinal (GI) bleed, electrolyte abnormalities, constipation, and dehydration. As with congestive heart failure (CHF), identification of the precipitant is paramount.

Although hepatic encephalopathy is generally considered to be a diagnosis of exclusion,⁸ an encephalopathic patient with a clear precipitant and good response to treatment can often be assumed to have hepatic encephalopathy. The role of routine investigations such as imaging, lumbar puncture, and electroencephalogram should be limited to patients not responding to treatment or with clinical suspicion of other causes of mental status change such as fevers, focal neurologic findings, or seizures. The differential diagnosis of altered mental status in chronic liver failure is wide and includes meningitis/encephalitis, septic encephalopathy, medication/alcohol withdrawal, Wernicke encephalopathy, psychoactive medications, and uremia.

Serum ammonia levels are often used in the evaluation of hepatic encephalopathy. While some correlation between severity of hepatic encephalopathy and level of serum ammonia does exist,⁹ several caveats bear mentioning. Ammonia poorly predicts the grade of encephalopathy¹⁰; therefore, an elevated level supports, but does not exclusively establish, the diagnosis. A normal level (20–70 mcg/dL) decreases the likelihood of hepatic encephalopathy, and should prompt considerations of further workup.

Treatment of Hepatic Encephalopathy

The treatment of hepatic encephalopathy plays both a therapeutic and diagnostic role, as response to therapy supports the diagnosis. Traditionally, nonabsorbable disaccharides such as lactulose have been effective by acidifying the gut and facilitating the passage of ammonium via fecal excretion.¹¹ For patients who do not tolerate lactulose or who do not produce adequate stool with lactulose alone, there may be utility to polyethylene glycol, which can exert a cathartic effect on the bowel if a patient does not have a mechanical obstruction of the bowel.¹² Recently, rifaximin has become an increasingly commonly used addition to lactulose, and has been shown to be more effective than lactulose alone.¹³

Flumazenil can cause a short-term improvement in symptoms of hepatic encephalopathy.¹⁴ Although an effect recovery or survival has not been shown,¹⁵ it can be considered in select situations such as supporting a diagnosis of hepatic encephalopathy, facilitating complete history, or allowing for goals of care discussions.

MANAGING RESPIRATORY STATUS AND PULMONARY COMPLICATIONS

General Considerations

Respiratory complications in chronic liver failure are very common and can be a frequent cause of decompensation. In the majority of cases, these manifestations are related to chronic conditions not specific to liver disease (chronic obstructive pulmonary disease [COPD], pneumonia, and pulmonary edema) or due to aspiration and the inability to protect the airway as a result of hepatic encephalopathy. However, several distinct pathologic processes that are unique to liver disease should be considered.

Respiratory Complications Related to Liver Disease

Perhaps the most common of these mechanisms is the direct effect of extrapulmonary fluid, either in the form of pleural effusions or ascites impacting the mechanics of the diaphragm. Large pleural effusions are commonly referred to as hepatic hydrothorax when they are greater than 500 mL and cannot be attributed to lung or heart dysfunction.¹⁶ Several mechanisms have been proposed, the prevailing explanation being direct transport of abdominal fluid through congenital diaphragmatic defects.¹⁷ The vast majority of these effusions are right-sided, although left-sided or bilateral effusions can exist in 15% of cases.¹⁸

Management of symptomatic hepatic hydrothorax usually involves placement of a pigtail catheter on the affected side to improve lung mechanics and for further workup through fluid analysis.¹⁷ However, there exists a high likelihood of recurrence; thus, this action should also be accompanied by attempts to correct the underlying cause through optimization of nutrition, salt restriction, and diuresis as tolerated.¹⁹ Thoracic surgery referral can be considered, although the preferred management of refractory hepatic hydrothorax remains transjugular portosystemic shunt (TIPS).²⁰

Pulmonary Vascular Complications

Hepatopulmonary syndrome and portopulmonary hypertension are two related yet pathologically distinct complications, which should always be considered in patients with respiratory issues.²¹ In both cases, the high cardiac output of liver disease causes sheer stress on the pulmonary vasculature, resulting in either pulmonary remodeling and elevated pulmonary pressures (portopulmonary hypertension) or pulmonary vasodilation and mismatch of perfusion and ventilation (hepatopulmonary syndrome).²²

Workup for pulmonary vascular complications begins with an echocardiogram. Right-heart overload raises suspicion for portopulmonary hypertension, while demonstration of an intrapulmonary shunt with contrast bubble echocardiography suggests hepatopulmonary syndrome.^{23,24} The definitive treatment in both cases is liver transplantation, but

vasodilators are often employed as a bridge to transplant in the case of portopulmonary hypertension. Patients presenting with a prostaglandin pump may present hypotensive, and consultation with pulmonology may aid in the decision to discontinue the pump.

CARDIOVASCULAR ISSUES

How to Manage Hemodynamics and Cardiovascular Complications

Hemodynamics can be difficult to manage in the chronic liver failure patient due to the complicated interplay between the cardiovascular and hepatic systems. Liver disease can precipitate heart failure through a phenomenon termed cirrhotic cardiomyopathy,²⁵ while right ventricular failure can precipitate cirrhosis through congestive hepatopathy and fibrosis.²⁶ Additionally, liver disease can have hemodynamic consequences, causing autonomic activation leading to low peripheral resistance and high output heart failure.²⁷

Blood pressure can normally run low; however, firm documentation of baseline blood pressures should always be sought, as few cirrhotics have systolic blood pressures persistently less than 85 mm Hg. Importantly, a broad differential diagnosis for hypotension other than vasodilation of liver disease should always be considered to include sepsis, hypovolemia, cardiomyopathy, tamponade, and adrenal insufficiency. Volume status may be difficult to establish in chronic liver failure, as patients are often total body volume overloaded, while intravascularly volume depleted. Bedside echocardiography can help to assess intravascular volume status, identify cardiogenic shock due to cirrhotic cardiomyopathy, and recognize tamponade physiology due to pericardial effusions secondary to fluid retention of liver failure.²⁸ Adrenal insufficiency can complicate advanced liver failure; correction results in improved rates of shock resolution and high survival rate.²⁹

Lactate is a marker of severity of illness and can be used as an endpoint of resuscitation. Lactate is cleared at a slower rate in chronic liver failure.³⁰ However, a high lactate is *never* normal and compensated cirrhotics have a normal lactate.³¹ Central venous oxygen saturation is expected to be high due to the high output state of liver failure; therefore, a low saturation should prompt consideration of other disease processes.

GASTROINTESTINAL MANIFESTATIONS

Varices and Bleeding Complications

One of the most catastrophic complications of chronic liver failure is GI bleeding. Liver failure increases the risk for GI bleed due to inherent coagulopathy, thrombocytopenia, risk of stress ulcers, and frequent gastric instrumentation. There are many potential causes of GI bleed in this population, including portal hypertensive gastropathy, gastric and duodenal ulcers, and arteriovenous malformations. However,

variceal bleed should always be considered due to the devastating course and unique therapeutic challenges.

The management of upper GI bleed in a cirrhotic is analogous to the management of chest pain in the ED—its presentation should lead to a more or less automatic, protocolized method of care with speed and steps titrated to acuity. This systematic approach should include access with large-bore peripheral IVs or a central catheter when peripherals are insufficient or not feasible, fluid and packed red blood cell administration when hemodynamic instability is present, and frequent hemoglobin checks. All GI bleeds should be started on a proton pump inhibitor (PPI) drip. Octreotide should be initiated whenever varices as a cause of GI bleeding are suspected, as it improves the efficacy of endoscopic therapy to control bleeding,³² especially if employed earlier.³³ Fresh frozen plasma (FFP), cryoprecipitate, platelets, and vitamin K are indicated for coagulopathic and thrombocytopenic patients. Once bleeding is controlled and the patient is more stable, overtransfusion should be avoided, as a restrictive hemoglobin transfusion threshold of 7 g/dL improved outcomes over a more liberal threshold of 9 g/dL.³⁴

Intubation prior to endoscopy is frequently performed. While routine intubation has not been shown to change the frequency of aspiration pneumonia or cardiopulmonary events, it should be considered in patients at risk of massive aspiration,³⁵ those who may not tolerate conscious sedation, and in hemodynamic instability. Our practice is to routinely intubate prior to endoscopy in any patient at risk for variceal hemorrhage. Esophagogastroduodenoscopy (EGD) plays a role in both diagnosis and management of GI bleed. EGD may be delayed pending further resuscitation; however, early EGD is associated with reductions in both length of stay and recurrent bleeding.³⁶

Because 20% of patients with variceal bleeding will develop spontaneous bacterial peritonitis, prophylactic antibiotics are often administered.^{37,38} A 7-day course with an extended spectrum penicillin, fluoroquinolone, or third-generation cephalosporin covering enterics is likely sufficient.

TIPS and balloon tamponade are two therapies that should be considered in the case of severe bleeding, hemodynamic instability, bleeding refractory to other interventions when no endoscopist is available, or for transport. TIPS reduces portal pressures and prevents variceal rebleed.³⁹ In patients with Child-Pugh Class C or Class B with active bleeding at endoscopy, early TIPS within 72 hours has been shown to reduce mortality.⁴⁰ Balloon tamponade is a potentially lifesaving intervention that can be done immediately if massive bleeding or hemodynamic instability exists. Perhaps the most serious complication is inflation of the gastric balloon in the esophagus causing esophageal rupture.⁴¹ Placement should always be confirmed with x-ray prior to full insufflation unless death is imminent.

Management of Ascites

Ascites is a common complication of chronic liver failure, with management often relegated to the outpatient setting.

However, massive ascites can cause respiratory difficulty due to mechanical compression of the diaphragm, abdominal compartment syndrome, and hemodynamic changes due to decreased venous return.⁴² While outpatient management usually centers on serial large-volume paracenteses and diuresis,⁴³ these should be used with caution in the case of critically ill patients presenting to the ED, due to the high susceptibility to renal failure and hemodynamic instability.⁴⁴ Temporary insertion of a pigtail catheter can allow for intermittent removal of fluid, with slower rates of drainage in patients who are hypotensive or clinically decompensated. Decreased urine output should prompt a slower rate of fluid removal. Hypotension can often be managed with intermittent fluid boluses. Albumin is often used with large-volume paracentesis, although the level of evidence in critically ill patients is relative.⁴⁵

RENAL AND ELECTROLYTE COMPLICATIONS

Electrolyte and Fluid Management

Fluid management in liver failure can be challenging due to the propensity of cirrhotics for clinical volume overload with intravascular depletion. Choice of resuscitation fluid varies between practitioners, with many practitioners preferentially using albumin in this population. There is currently no consensus between the benefits of crystalloids versus colloids in the chronic liver failure population.

Hyponatremia is commonly seen in cirrhotics⁴⁶ and is an independent predictor of mortality in this population.⁴⁷ Correction in symptomatic patients should be done with caution, as this population is also particularly vulnerable to central pontine myelinolysis (CPM), even with relatively modest elevations in sodium in this population. Frequent sodium monitoring should be done, especially in the setting of large-volume resuscitation.⁴⁸ Balanced electrolyte solutions should be used if possible; otherwise, the intermittent addition of ½ normal saline can be used if sodium levels rise too precipitously.

Kidney Injury in Liver Failure

Acute kidney injury is very common among critically ill patients with chronic liver disease. Potential etiologies commonly seen in chronic liver disease include hypovolemia, acute tubular necrosis, abdominal compartment syndrome, low flow states due to vasoplegia and sepsis, and hepatorenal syndrome (HRS). HRS, which is caused by splanchnic vasodilatation leading to renal vasoconstriction, may represent a very common cause of renal injury in patients with cirrhosis and ascites.⁴⁹

Liver transplant is the only definitive therapy for HRS; however, vasoconstrictors such as midodrine and octreotide are commonly used as a temporizing measure due to their presumed effect on splanchnic vasodilation.⁵⁰ Renal replacement therapy can be offered in limited cases⁵¹; however, it neither has been shown to improve HRS nor has it been

associated with improved outcomes, and discussions on risks/benefits as well as goals of care should precede initiation.

HEMATOLOGIC CONSIDERATIONS

Chronic liver failure is associated with multiple hematologic abnormalities, including anemia, thrombocytopenia, and coagulopathy. The coagulopathy of liver disease involves a decrease in both procoagulant and anticoagulant factors produced by the liver,⁵² resulting in a hemorrhage or thrombosis at any time depending on clinical circumstances. These baseline abnormalities can complicate the management of patients already prone to bleeding complications and in need of invasive interventions.

Coagulation status can be difficult to quantify as prothrombin time/international normalized ratio (INR) measures thrombin needed to form an initial clot but not the thrombin inhibited by anticoagulant drivers.⁵³ Therefore, a high INR overestimates the degree of coagulopathy, making a patient with chronic liver failure and a given INR much less likely to bleed than a comparable INR due to warfarin administration or other causes. While the bleeding patient often is treated with factors to correct the INR, other mechanisms to explain the hemorrhage—such as portal hypertension, renal failure, and bacterial infections—should be considered and addressed.⁵⁴

Thrombocytopenia is a common finding in chronic liver failure,⁵⁵ observed in a majority of patients, and is often used as a marker of advanced disease.⁵⁶ The decrease in platelets is likely due to several mechanisms, including splenic sequestration, bone marrow suppression, medication effect and decreased thrombopoietin production by the liver.⁵⁷

Management of Bleeding and Bleeding Risk

Management of bleeding risk should be done with caution. While cirrhotics are prone to bleed, the degree of coagulopathy is overestimated by the INR and overcorrection can increase the susceptibility to thrombotic events. In the case of thrombocytopenia, low platelet counts are offset by improvement in platelet function due to elevated levels of von Willebrand factor and fewer platelets needed due to preserve thrombin generation.⁵⁸

Correction varies by clinical situation and indication. FFP should be given only for active bleeding while pooled platelets should be given for platelet counts less than 10,000/mm³. Platelet count can be expected to increase by 20,000/mm³ for every unit of pooled platelets transfused.⁵⁹ An INR reduction from 3.0 to 2.0 requires 2 to 4 units of FFP, although more may be frequently required.⁶⁰ Vitamin K can reasonably be given for at least one dose.⁶¹

Management of Thrombosis

Partly due to the tendency for thrombosis, there is a significant incidence of deep vein thrombosis (DVT) independent of

INR and platelet counts.⁶² In those patients requiring full anticoagulation for venous thromboembolism, heparin is the anticoagulant of choice. The coagulopathy of liver disease can have a heparin-like effect,⁶³ decreasing the reliability of aPTT measurements. Therefore, anti-Xa levels can assist with titration.⁶⁴

INFECTIOUS DISEASE COMPLICATIONS

Susceptibility to Infection

Infectious complications are very common, with 30% to 50% of chronic liver failure patients either presenting with an infection at the time of presentation or acquiring one during their hospital stay.⁶⁵ Moreover, bacterial infections alone cause 25% of deaths in this population.⁶⁶ The vulnerability of this population to infection is multifaceted, including impaired immunity, frequent hospitalizations, and need for catheters and invasive procedures.

Due to this vulnerability, practitioners should maintain a low threshold for infectious workup for altered mental status and tachypnea, recognizing that the absence of fever and leukocytosis is insufficient to rule out infection in this population. In addition to standard cultures and workup, special consideration should be given to the possibility of spontaneous bacterial peritonitis (SBP), which remains a common, yet insidious, cause of infection.⁶⁷ Any clinically decompensated patient with ascites should undergo paracentesis and fluid analysis, unless clinically unable to tolerate the procedure. Abdominal CT is not a routine part of the workup unless used to differentiate secondary and primary peritonitis.

Management of Sepsis and Infectious Complications

Early and appropriate antibiotics administration is the cornerstone of management of infectious complications even if the source is not immediately known. In the case of suspected SBP, a third-generation cephalosporin or extended spectrum penicillin is generally first line. For patients with suspected SBP and elevated creatinine, bilirubin, or BUN within 6 hours of presentation, the addition of 1.5 g/kg albumin may provide additional benefit.⁶⁸

Management of sepsis and septic shock remains identical to the management of patients without liver failure, with special consideration to specific sepsis-related complications to which this population remains particularly vulnerable, such as hypoglycemia, hypothermia, and adrenal insufficiency.⁶⁹

HOW TO PUT IT ALL TOGETHER: TRANSFERRING TO A TERTIARY CARE/REFERRAL CENTER

Critically ill patients with chronic liver failure are often identified for transfer to a higher level of care, especially to a transplant center. Reasons for transfer include complexity of

disease, lack of on-site specialists or capabilities, consideration for transplant, or continuity of care if a specialist regularly follows the patient in the outpatient setting. Early recognition of the patient who will benefit from transfer is paramount, and can often be triaged from the ED. Preparations prior to transfer include airway management if there is any consideration that the patient may lose the ability to protect the airway during transport, adequate IV access, and clear documentation of workup done with reasons for transfer to a higher level of care.

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Acute Pancreatitis

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INTRODUCTION

Acute pancreatitis (AP) is a frequent diagnosis encountered in the emergency department (ED), and is a common disease of the gastrointestinal system. The incidence of AP varies between 4.9 and 73.4 cases per 100,000 worldwide, affecting men and women equally.^{1,2} The clinical manifestations can vary from mild disease, in which there is involvement of the local pancreatic tissue, to progression into necrosis of the pancreas and multiple organ failure. Approximately 25% of patients with AP develop severe disease with associated multiple organ failure, and require admission to the intensive care unit (ICU).³

Physicians often encounter challenges in adequate identification of the subset of patients that will progress into severe acute pancreatitis (SAP).

EPIDEMIOLOGY

The majority of the patients diagnosed with pancreatitis in the ED suffer from mild uncomplicated disease. Swaroop et al.⁴ reported that, in the United States, approximately 210,000 patients are admitted every year for pancreatitis. Of these patients, 20% to 25% will develop SAP.^{3,4} SAP alone carries a mortality that ranges from 20% to 40% despite ICU admission and aggressive management.⁴ Alcohol abuse and gallstone disease are the two most common causes that account for approximately 70% to 80% of the cases.⁵ Most of the patients will exhibit interstitial pancreatitis rather than necrotizing pancreatitis (85% vs. 15%).⁵ Organ failure occurs more frequently in patients with necrotizing pancreatitis rather than in the interstitial type (50% vs. 5%–10%). Thus, mortality is going to be higher in that subset of patients

(17% vs. 3%).⁵ Infected necrosis will affect 15% to 20% of the necrotizing pancreatitis population.⁵

PATHOGENESIS

The exact mechanisms that trigger the process involved in AP continue to be somewhat poorly understood. As a general rule, the pathways that lead up to the disease are divided into three phases. First, there is activation of trypsin within the pancreatic acinar cells. During the second phase, inflammation within the pancreatic parenchyma ensues. Last, in the third phase, there is extrapancreatic inflammation that may involve remote organ systems, for example, the lungs, heart, and kidneys. The majority of cases of AP are mild, but in 10% to 20% of the patients, the pathways leading to intra- and extrapancreatic inflammation result in systemic inflammatory response syndrome (SIRS). During SIRS, there is massive and uncontrolled release of cytokines and pancreatic enzymes, which may predispose to multiple organ failure and pancreatic necrosis.^{5,6}

CLASSIFICATION

The Atlanta classification of pancreatitis was originated in 1992 as an attempt to offer a universal consensus for the classification and definition of pancreatitis. This classification was revised in 2012; some definitions were modified for a better stratification of the patients and better classification of the severity of the disease. Table 26-1 contains the Atlanta Classification.

In order to establish the diagnosis of pancreatitis, the patient must exhibit at least two of the following three


TABLE 26-1: Atlanta Classification of Pancreatitis

Mild acute pancreatitis
No organ failure
No systemic complications
Moderately severe acute pancreatitis
Transient organ failure that lasts < 48 hours, and/or
Local or systemic complications without persistent organ failure
Severe acute pancreatitis
Persistent organ failure > 48 hours
Single or multiple organ failure

findings: (1) abdominal pain, (2) serum lipase elevation at least three times the upper normal limit, and/or (3) morphologic evidence of pancreatitis in imaging studies such as computed tomography (CT) scan, magnetic resonance imaging (MRI), or ultrasound.^{7,8} Almost half of the patients presenting to the ED with pancreatitis will complain of having acute onset epigastric abdominal pain that radiates to the back.⁵ The patients may describe the pain as acute in onset, unbearable, lasting at least 24 hours without relief, and often associated with nausea and/or vomiting. For history purposes, documentation and time tracking of the disease, the onset of acute pancreatitis is defined as the time of onset of abdominal pain, not the time of admission to the hospital.⁷ There are two types of AP: interstitial edematous and necrotizing pancreatitis. Clinically, AP will manifest as two different phases, early (within 1 week) and late (> 1 week) usually accompanied by local complications.⁸ The presence of remote organ failure will determine the severity of the disease.⁸

Interstitial edematous pancreatitis, which accounts for the majority of the cases of AP, is a diffuse and localized enlargement of the pancreas secondary to inflammation and edema. There is intact perfusion throughout the pancreatic parenchyma. CT scan may show a homogeneous distribution of the inflammatory changes, peripancreatic fat stranding, and fluid. The clinical manifestations usually resolve within the first week.⁷

Necrotizing pancreatitis is characterized by necrosis of the pancreatic parenchyma and the peripancreatic tissues. The natural evolution of the progression of the necrosis may take up to several days, which explains why early CT scanning may not provide accurate information about the extent of hypoperfusion throughout the pancreatic parenchyma. The necrosis may be variable as it can remain solid or liquefy, persist as a sterile collection, become infected, or disappear over time.⁷ Infection of pancreatic necrosis is a rare occurrence, but when it occurs, it can exponentially increase the morbidity and mortality of the AP patient. Infected necrosis can be assumed when there is evidence of gas within the pancreas in the peripancreatic tissues in CT scan, or when there is a positive Gram stain or culture from a percutaneous aspiration of the pancreatic fluid or tissue.

The Atlanta classification defines three different degrees of severity of AP based on organ failure and the extent of local

complications: mild AP, moderately severe AP, and severe AP. Organ failure is defined as transient (less than 48 hours), or persistent (more than 48 hours).⁷ Local complications include peripancreatic fluid collections, necrosis (sterile or infected), pseudocysts, and walled-off necrosis.^{7,8} In mild AP, there is no evidence of organ failure or systemic complications. The mortality is low, and these patients usually get discharged home during the early phase. Moderately severe pancreatitis encompasses the patients that have evidence of transient organ failure, and local or systemic complications without persistent organ failure. When organ failure becomes persistent, more than 48 hours of duration, this is considered SAP. Mortality has been reported to be as high as 36% to 50%.⁷ Establishing the severity of the pancreatitis on admission can pose challenges because, if the patient presents with organ failure, it is difficult to predict if this is going to be transient versus persistent. It is advised to re-evaluate the status of the patient at 12, 24, and 48 hours and, within 7 days of admission.⁷

INITIAL EVALUATION

During the primary assessment in the ED, it is essential to remember that the presentation of AP can vary from a mild case of epigastric abdominal pain to a patient who appears toxic and presents with multiple-organ failure or even septic shock. The most important thing to keep in mind is to include AP in the differential diagnosis of the adult patient that presents to the ED complaining of epigastric abdominal pain, SIRS, and/or even shock. The differential diagnoses should always include mesenteric ischemia, ulcer perforation (gastric or duodenal), biliary disease, abdominal aortic aneurysm, intestinal obstruction, or even inferior wall myocardial infarction (MI).⁵ Relevant clues that should be inquired about in the history are past abdominal surgeries, previous biliary or pancreatic disease, alcohol abuse, recent abdominal trauma, current medications, symptoms associated with malignancy, and family history. The physical exam should include a thorough abdominal evaluation, paying close attention to the location of the tenderness, presence of distention, and skin discoloration changes. The Grey Turner sign, which is hemorrhage in the retroperitoneal space, may manifest as bruising or purple discoloration along the flanks of the patient. Cullen's sign may also accompany the skin changes due to bleeding or bruising of the periumbilical subcutaneous and fatty tissue. Both of these signs may take up to 24 to 48 hours to develop and may be predictive of the development of SAP with a hemorrhagic component. Limited bedside ultrasonography can serve as an adjunct and can offer additional information during the initial abdominal examination. It can offer clues regarding the presence of a biliary calculus, fluid collection, ascites, and/or abdominal aorta aneurysm. Disadvantages of ultrasound is that it is operator dependent, and the results may be preliminary, as not all emergency physicians have official certification for interpretation of the images obtained. It can provide data to guide the workup, especially when encountered with a hemodynamically unstable patient. In terms of predicting

severity of disease, there are two scores that have been useful in AP, the Acute Physiology and Chronic Health Evaluation (APACHE-II) and the Ranson criteria. The APACHE-II score has been correlated with accurate prediction of severity of AP, and it can be reassessed on a daily basis.^{5,9} The Ranson criteria have proven to be disadvantageous in the ED setting because, in order to complete the evaluation for outcome prediction, a full 48 hours is required.⁵

DIAGNOSTICS

When evaluating the patient for suspected AP, the laboratory data should include a complete blood count, basic metabolic panel, liver function tests, and a serum amylase and lipase. Serum lipase has been found to be more specific and remains elevated longer than amylase.^{5,7,8} Diagnostic transabdominal ultrasound should be obtained in every patient with AP as an investigation for biliary calculi.⁸ Negative ultrasound results should prompt the ED physician to consider other differential diagnoses as the cause for AP, for example, passage of a biliary stone, alcohol abuse, hypertriglyceridemia, and pancreatic mass.

CT scan of the abdomen as a modality for diagnosis of AP in the ED can underestimate the severity of disease in the early phases because it may take several days for differentiation of the pancreatitis to evolve.⁵ CT scan is usually reserved for cases of undifferentiated abdominal pain to evaluate for other diseases.⁸ The Balthazar computed tomography score index (CTSI) was developed in 1990 as a tool for evaluation of the severity of AP based on morphologic imaging appearance.⁹ CT scan of the abdomen and pelvis should be performed with intravenous (IV) contrast to investigate for two things: evaluation of the extent of pancreatic and extrapancreatic inflammation, and to assess for pancreatic necrosis.⁹ Findings suggestive of pancreatic necrosis can be visualized as lack of IV contrast uptake through the pancreatic parenchyma, and heterogeneity throughout the tissues. Table 26-2 contains the Balthazar CT grading system. Despite CT scan findings, clinicians must always take into consideration that the presence of organ failure carries more weight on the morbidity and mortality of these patients than the extent of pancreatic necrosis.⁵

Another imaging modality is magnetic resonance cholangiopancreatography (MRCP), which has the ability to detect choledocholithiasis as small as 3 mm in diameter. Also, it provides information regarding the extent of pancreatic necrosis.⁸ An advantage of MRCP is that it is noninvasive, and in patients with contrast allergy or even acute renal

failure, it can provide useful information regarding pancreatic structural damage.

MANAGEMENT

The mainstay of the management of AP during the initial phases of admission to the ED consists of supportive measures, paying special attention to adequate fluid resuscitation and analgesia.¹⁰ While in the ED, it can be challenging to identify those patients that will progress to deteriorating during their hospitalization. In the early stages of the disease, surgery is usually not indicated, but when emergency surgical intervention is required, there is an associated mortality of 40% to 78%.¹¹⁻¹³ Possible indications for surgery could be evidence of perforation, ischemic viscus, or decompressive laparotomy in the case of abdominal compartment syndrome secondary to massive fluid resuscitation.¹⁰

The role of fluid resuscitation during the first 12 to 24 hours of the diagnosis of AP plays a crucial role in the prevention of hypovolemia secondary to different factors: fever, sweating, tachypnea, vomiting, decreased oral intake, and third spacing fluid losses. It is thought that the microcirculatory effects of inflammation within the pancreatic parenchyma causes edema and reduces blood flow, which leads to cell death, necrosis, release of pancreatic enzymes, and activation of inflammatory cascades.⁸ The inflammation itself increases vascular permeability and third spacing ensues, leading to worsening of pancreatic hypoperfusion, which can lead to necrosis. By providing intravenous hydration, the micro- and macro-circulations are maintained and supported to potentially prevent progression to necrosis.⁸ It can be very challenging to determine what kind of fluid to give and how much. A recent systematic review reported no clinically significant differences between fluid resuscitation between crystalloids versus colloids.¹⁴ Although there are no strong recommendations, goals for fluid resuscitation should be established. Urine output, heart rate, blood pressure, central venous pressure (CVP), lactate, mixed venous oxygen, base deficit, hematocrit, and blood urea nitrogen (BUN) are parameters followed.¹⁵ Studies have shown that BUN correction offers no advantage to improving outcomes.¹⁶ CVP was shown to be inaccurate when used as a sole goal for resuscitation, as it led to inappropriate use of inotropes or vasopressors. A low CVP can be helpful when encountered with a patient with suspected hypovolemia and/or oliguria. Hematocrit has been shown to increase in the setting of hypovolemia secondary to third spacing and reductions in intravascular volume. This can result in a reduction of pancreatic blood flow, which can also lead to pancreatic necrosis.⁵ The hematocrit goal poses some controversy. While studies have shown that hematocrit levels of > 44% have been associated with pancreatic necrosis,¹⁸ it has also been reported that, when hematocrit is lowered to < 35% too quickly, there is an elevated rate of sepsis and even death.¹⁹ Clinicians usually target a urine output of 0.5 mL/kg/h; however, there have been reports of an inconsistent relationship between renal perfusion and urine output in critical illness.²⁰ Rather than targeting all those mentioned



TABLE 26-2: Balthazar CT Grading System^{5,9}

A	Normal pancreas
B	Pancreatic enlargement
C	Pancreatic inflammation and/or peripancreatic fat stranding
D	Single peripancreatic fluid collection
E	2 or more fluid collections and/or retroperitoneal air

parameters separately, each clinician should individualize each patient and analyze the patient's fluid status taking into consideration vital signs, measurements, and laboratory values as a group. The World Congress of Gastroenterology guidelines recommend a rapid initial crystalloid bolus to correct base deficit within the first few hours of monitoring vital signs and urine output. Then, the recommendation is 35 mL/kg per day, plus extra boluses required to replace ongoing third space losses.²¹ Of note, patients that do not respond to aggressive fluid resuscitation within the first 6 to 12 hours may not benefit from ongoing high volumes of intravenous fluids.⁸ There are no definitive recommendations regarding the type of fluid to infuse, but studies have reported that lactated Ringer's solution appears to be more beneficial, resulting in fewer patients that developed SIRS as compared with patients that received normal saline 0.9%, leading to better electrolyte balance and improved outcomes.¹⁶ Also, low pH in normal saline 0.9% solution is theorized to activate trypsinogen, and makes acinar cells vulnerable to injury and potentially increases the severity of the AP.¹⁶ Normal saline 0.9% solution carries a salt load that it is theorized takes a patient approximately 2 days to get rid of.²² It has also been demonstrated that a 2 L bolus of normal saline 0.9% solution decreased renal artery blood flow velocity and renal cortical perfusion when compared to an infusion of 2 L of Plasmalyte, which is a more physiologic crystalloid solution with a normal pH.¹⁵

A good approach to initially resuscitate the subset of patients who present to the ED with evidence of SAP and hypovolemia or even shock is to establish institutional protocols as an attempt to standardize management. It is imperative to ensure adequate IV access, and physicians should have a low threshold for placement of central and arterial lines for possible hemodynamic monitoring. For example, in our institution, the SAP patient with a MAP of less than 65 mm Hg will be resuscitated with up to 3 L of Plasmalyte; then, if the MAP continues to be less than 65 mm Hg, norepinephrine infusion is started. If the patient continues to be fluid responsive, another liter of crystalloid may be added. Upon starting the norepinephrine infusion, if the requirement exceeds 10 mcg/min, vasopressin is started. Measurement of serum albumin is performed; if the level is less than 2.5, then an albumin bolus may be administered. A central venous oxygen saturation can be obtained; if it is less than 70%, the patient is ordered an echocardiogram and/or connected to hemodynamic monitoring. At this point, an inotrope may be considered to improve oxygen delivery in the state of shock. Of note, it is very important not to over-resuscitate these patients in order to avoid potential complications of acute respiratory distress syndrome (ARDS) or abdominal compartment syndrome (ACS). Early use of vasopressors is indicated in the patient who has already received 3 to 5 L of fluid resuscitation and is not fluid responsive.

Special attention should be focused on patients diagnosed with SAP that are transferred to the ED from another institution that have already been "partially" treated with fluid resuscitation. It is important to keep track of the total fluid administered. ACS is a known complication of massive fluid or blood component resuscitation in the setting of SAP. ACS is a steady state of increased intra-abdominal pressure

(IAP) and it is defined by an IAP of > 20 mm Hg that is associated with new organ dysfunction/failure: for example, acute renal failure, bowel ischemia, and/or shock liver.²³ In the case of this diagnosis, the treatment is emergent decompressive laparotomy, in which the fascia is incised and left open to relieve the IAP and a temporary abdominal closure is performed.

Antibiotics

The mortality rate of SAP with sterile necrosis is approximately 10%, increasing to 25% in the setting of infected pancreatic necrosis.²⁴ The current recommendations disfavor the routine use of prophylactic antibiotics in patients with SAP or in patients with sterile necrosis to prevent the development of infected necrosis.^{24–26} Empiric use of antibiotics should be considered when encountered with a patient with evidence of an extrapancreatic infection such as cholangitis, urinary tract infection (UTI), undifferentiated septic shock, or a patient with SAP with evidence of necrosis and/or peripancreatic gas in the initial CT scan who fails to improve after initial resuscitation.⁸ The antibiotics of choice are carbapenems, quinolones, and metronidazole.⁸

Nutrition

The majority of patients in the ED setting exhibit abdominal pain, nausea, and/or vomiting. Symptomatic and supportive treatment should be provided. As a result, there is decreased oral intake. As soon as the patients are able to tolerate oral nutrition, it should be restarted and encouraged. Upon admission, nutritional support may not be required because the course of the disease may resolve with short-term bowel rest, fluid administration, and analgesia. The SAP population are known to become hypermetabolic, and by the second week of the disease, they become protein depleted secondary to the high catabolic rate.²⁷ Enteral feedings are known to decrease the cytokine cascade as well as maintain the integrity of the gastrointestinal mucosa. Issues with decreased gastric tolerance of enteral feeds are commonly encountered in the SAP population. The American Society of Parenteral and Enteral Nutrition recommends that all patients with SAP complicated by organ failure and/or pancreatic necrosis should have a postpyloric (preferably nasojejunal) feeding tube within the first week of hospitalization. The following goals for nutritional support should be achieved: treat and prevent gastric outlet obstruction, prevent aspiration, start early enteral feedings, prevent ileus, restore gut function, and potentially suppress organ failure.²⁷

Endoscopic Retrograde Cholangiopancreatography (ERCP)

The majority of the gallstones that cause pancreatitis pass spontaneously to the duodenum and are eliminated in the stool. However, there is a small subset of patients in which gallstones do not pass. They have persistent choledocholithiasis, which can progress into pancreatic duct and/or biliary tree obstruction, leading to SAP and/or cholangitis. ERCP has been proven to improve outcomes in these patients by reduc-

ing complications when performed within the first 24 hours of admission.^{8,28} In those patients with gallstone pancreatitis without clinical or laboratory evidence of an ongoing obstruction, ERCP is not needed in the emergent setting.⁸ Whenever there is suspicion of choledocholithiasis without evidence of cholangitis, patients may undergo MRCP or even endoscopic ultrasound (EUS) for further evaluation.

The Role of Early Surgery in AP

There is very little role for emergency surgery early in the course of AP. Today, operative management of AP is limited to two complications of pancreatitis: ACS due to aggressive volume resuscitation, and infected peripancreatic collections with concern of bowel ischemia or perforation. Hemorrhagic pancreatitis is now managed by interventional radiology (IR) embolization. In the setting of symptomatic patients with pseudocysts, sterile or infected necrosis (pancreatic or extra-pancreatic), minimally invasive methods such as percutaneous drainage are preferred as a first approach instead of open surgical debridement.⁸

CONCLUSION

The majority of the AP cases encountered in the ED are going to be mild, but when treating a SAP patient, it is extremely important to recognize it as soon as possible and to start immediate resuscitation with a goal to reestablish intravascular volume, treat pain, and work toward the resolution of shock. Patients that present to the ED with undifferentiated abdominal pain and lack laboratory data to diagnose AP should have imaging studies ordered, preferably an abdomen/pelvis CT scan with IV contrast. If the diagnosis of AP is established with elevated lipase and abdominal pain, an abdominal ultrasound should be obtained to rule out gallstones as the cause of the AP. In the setting of shock and/or organ dysfunction, it is important to optimize the volume status. Utilization of echocardiography or hemodynamic monitoring may be very helpful to direct goals of resuscitation. Blood parameters such as lactate, hematocrit, and central venous oxygen should be optimized with either fluids, albumin, blood transfusion, vasopressors and/or inotropes. Special attention should be paid to avoid over-resuscitating these patients with massive amounts of fluids in the setting of volume unresponsiveness. For disposition purposes, surgery and critical care should be consulted as soon as the initial diagnostic studies and resuscitative efforts are made.

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Acid–Base Disorders

Kevin M. Jones • William C. Chiu

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The assessment of an emergency patient's acid–base status must begin with a clinical suspicion that an underlying acid–base disorder exists. That an acid–base disorder might exist in a patient presenting obtunded, hypotensive, hypoperfused, or obviously in extremis is rarely surprising. Patients with more subtle presentations or chronic, well-compensated acid–base disorders often elude clinicians in today's busy and overtasked emergency departments (EDs). One must remain diligent for clinical signs, astutely reviewing basic electrolyte panels, and remain open to the possibility that patients may be or become more ill than they first appear. Knowing when to investigate for the possibility of an acid–base disorder or evaluate for complex mixed acid–base disorders requires astute clinical acumen. Unfortunately, many emergency providers today lack the ability to perform mixed acid–base assessments with facility, and many mixed or complex disorders, no doubt, go undiagnosed or undertreated.

In this chapter, we hope to review the measures of acid–base status routinely available to emergency medicine critical care practitioners, their utility, as well as their liabilities. Using these measures, this chapter will provide a rational guide to the interpretation and initial management of a patient's acid–base status.

THE HENDERSON–HASSELBALCH EQUATION

The Henderson–Hasselbalch equation in its original form is of limited clinical utility, and is given as follows:

$$\text{pH} = \text{pK} + \log \frac{[\text{HCO}_3^-]}{[\text{H}_2\text{CO}_3]}$$

The Kassirer–Bleich equation is obtained by inserting known constants into the Henderson–Hasselbalch equation, then taking the antilog of each side.¹ The resultant equation is much more conceptually useful in understanding clinical acid–base interactions:

$$[\text{H}^+] = 24 \times \frac{\text{Pco}_2}{[\text{HCO}_3^-]}$$

The Kassirer–Bleich equation makes clear the interactions between the Pco_2 , the bicarbonate concentration, and the free hydrogen ion concentration. If any two of these values are known, the other can be calculated.

MEASURES OF ACID–BASE STATUS

Serum Bicarbonate

The serum bicarbonate concentration is often one of the first pieces of measured laboratory data available for clinical assessment of acid–base status. Regardless of how it is labeled when reported, this value is actually a measured total CO_2 concentration.² The total CO_2 concentration is a combination of bicarbonate, carbonic acid, and dissolved carbon dioxide. The amount of dissolved carbon dioxide can be calculated if the measured Pco_2 is known by multiplying the Pco_2 by the solubility coefficient of CO_2 in the blood, 0.03. Hence:

$$\begin{aligned} \text{“Bicarbonate concentration”} &= \text{total } \text{CO}_2 \\ &= [\text{HCO}_3^-] + [\text{H}_2\text{CO}_3] + (0.03)(\text{Pco}_2) \end{aligned}$$

Most of the time, the relative contribution of the Pco_2 to this value is negligible and, as such, is commonly ignored. It

can become a significant factor in the hypercapnic patient, leading to reported total bicarbonate levels higher than would be reflected by a true assessment of the $[\text{HCO}_3^-]$.

The reported serum bicarbonate can be a good initial indicator of the presence of an uncomplicated metabolic acidosis. As we can see from the Kassirer–Bleich equation, a rise in $[\text{H}^+]$ (decreasing pH) will necessitate an increase in the ratio of Pco_2 to $[\text{HCO}_3^-]$; this will usually show up as a decreased serum bicarbonate measure. Following repeated serum bicarbonate measures is often performed to record the response to treatment for simple organic metabolic acidoses, such as ketoacidosis or lactic acidosis, when simple and relatively noninvasive measures are desired, and when complex mixed acid–base disorders have been excluded.

Serum bicarbonate is, however, not a very sensitive measure, and does not allow on its own for an analysis of the underlying disorder. In the presence of hypercapnia, as mentioned earlier, it can be higher than anticipated with an underlying acidemia due to the contribution of the Pco_2 and respiratory compensation. Patients with chronic lung disease or metabolic compensation can have markedly elevated serum bicarbonates at baseline; without an appreciation for that baseline, a “normal” value can be falsely reassuring. Primary respiratory acidosis or alkalosis will produce a compensatory change in the bicarbonate levels, and can mask a mixed acid–base disorder. Reliance on the measured serum bicarbonate as a solitary measure of acid–base status should only be entertained in a simple patient without suspicion for underlying compensation and an unambiguous clinical picture.

Arterial Blood Gas

Arterial blood gas (ABG) remains the mainstay for acid–base interpretation. While not always necessary for the identification and management of an acid–base disorder, a thorough understanding of the reported values and how to interpret them is essential. Laboratories will report values for pH, Pco_2 , Po_2 , $[\text{HCO}_3^-]$, base excess (BE) (or deficit), and percent oxygen saturation.

The pH of the blood, normally between 7.35 and 7.45, is an assessment of the free hydrogen ion concentration in the blood. A blood pH of less than 7.35 is called *acidemia*; a blood pH of greater than 7.45 is called *alkalemia*. The pH is measured in the lab with an electrode permeable only to hydrogen ions.

The Pco_2 and Po_2 are the partial pressure of dissolved CO_2 and O_2 in the blood, respectively. They are also measured values obtained by using electrodes specific to the respective gasses.

The $[\text{HCO}_3^-]$, as reported with a blood gas, is calculated by using the measured pH and the measured Pco_2 using the Henderson–Hasselbalch equation. While some advocate that the measured $[\text{HCO}_3^-]$ (or total CO_2 concentration) as reported in an electrolyte panel is a more reliable figure, that measured value can be flawed for the reasons discussed earlier. It is doubtful that either the calculated or measured $[\text{HCO}_3^-]$ can uniformly be considered a more “true” assessment of

the serum $[\text{HCO}_3^-]$. One should be aware of the liabilities of each approach when attempting to interpret discrepancies between the two.

The BE is an estimation of the amount of acid it would take to titrate 1 L of blood back to a normal pH of 7.40, assuming that the Pco_2 were adjusted to a normal of 40 mm Hg. The BE is usually reported in units of milliequivalent per liter. It is calculated from the measured pH and the calculated $[\text{HCO}_3^-]$ according to the following equation³:

$$\text{BE} = 0.93 \times [\text{HCO}_3^-] + 13.77 \times \text{pH} - 124.58$$

In an acidosis, the BE is a negative value, and is often referred to as a *base deficit*. The BE is often used as a marker for metabolic acidosis, and is more reliable than the serum bicarbonate concentration as such, as it is adjusted for the effect of a concomitant respiratory disorder.

The *oxygen saturation* reported on a blood gas analysis is also a calculated value using the measured Po_2 and pH, based on the anticipated hemoglobin oxygen dissociation curve for that given pH.

AN APPROACH TO THE INTERPRETATION OF ACID–BASE DISORDERS

There is an important distinction to be made between *acidemia* and *acidosis*, as well as between *alkalemia* and *alkalosis*. *Acidemia* and *alkalemia* refer to the relative abnormalities in the blood pH. *Acidosis* and *alkalosis* refer to an underlying disease process. It is possible in mixed acid–base disorders to have a low pH, hence be *acidemic*, while having a concurrent metabolic *alkalosis*. An example of this might be an *acidemic* diabetic ketoacidosis patient with a low pH and a primary metabolic *acidosis*, who also has a concurrent metabolic *alkalosis* (but not *alkalemia*) brought about by vomiting and resultant hydrogen ion depletion.

What follows is a five-step approach to the interpretation of acid–base status^{2,4–8} (see Table 27-1). Whether this approach or another is used by an individual provider is not as important as is the practice that every assessment of acid–base status go through a sequenced and methodical analysis every time.

Step 1: Is there a primary acidemia or alkalemia? Look at the pH as determined by the blood gas. A pH of less than 7.35 demonstrates acidemia, while a pH of greater than 7.42 demonstrates alkalemia. The direction in which the pH is deviated from normal is the effect of the primary acid–base disorder affecting the patient. While compensation for the primary disorder will decrease the effect of the primary disorder, it will never bring the pH back entirely to a normal range.

Step 2: Is the primary disorder respiratory or metabolic? Look at the Pco_2 from the blood gas and the serum HCO_3^- . Whether to use the measured total bicarbonate from an electrolyte profile or the calculated HCO_3^- from a blood gas analysis remains a debate, although



TABLE 27-1: Five Steps of Acid–Base Analysis

- Step 1: Acidemia (pH < 7.35) or alkalemia (pH > 7.42)
- Step 2: Primary respiratory or metabolic disturbance? (Look at Pco₂ on ABG or [HCO₃])
- Step 3: Is there appropriate compensation for the primary disorder?
- Metabolic acidosis: Pco₂ = (1.5 × [HCO₃]) + 8 (± 2)
- Metabolic alkalosis: ↑ Pco₂ = 0.6 × ↑ [HCO₃] (± 2)
- Respiratory acidosis: ↑ Pco₂ 10, ↑ [HCO₃] by 1 (acute) or 4 (chronic)
- Respiratory alkalosis: ↓ Pco₂ 10, ↓ [HCO₃] by 2 (acute) or 5 (chronic)
- Step 4: Is there an anion gap metabolic acidosis (AGMA)?
- AG = [Na] – ([HCO₃] + [Cl]). If AG > 12, an AGMA is present
- Step 5: If metabolic acidosis, is there another concomitant metabolic disturbance?
- If **AGMA**, then calculate Δ Gap = Δ AG – Δ [HCO₃]
= (AG – 12) – (24 – [HCO₃])
- If Δ Gap is > 6, there is a combined AGMA and metabolic alkalosis
- If Δ Gap is ≤ 6, there is a combined AGMA and NAGMA
- If **NAGMA**, for every 1 mEq/L ↑[Cl], there should be 1 mEq/L ↓[HCO₃]
- If [HCO₃] decrease is less than predicted, then there is a combined NAGMA and metabolic alkalosis

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these authors, as a matter of routine practice, use the measured value from the electrolyte profile. In acidemia, a high Pco₂ suggests a primary respiratory acidosis, usually accompanied by an elevated [HCO₃] representing metabolic compensation. A low [HCO₃] suggests a primary metabolic acidosis, usually accompanied by a low Pco₂, representing a partial respiratory compensation. In alkalemia, a low Pco₂ suggests a primary respiratory alkalosis, usually accompanied by a low [HCO₃] representing a partial metabolic compensation. A high [HCO₃] suggests a primary metabolic alkalosis, usually accompanied by a high Pco₂, representing a partial respiratory compensation (see Table 27-2).

Step 3: Is there appropriate compensation for the primary disorder? In primary metabolic disorders, there should be rapid compensation for the resultant acidemia or alkalemia by the respiratory system.



TABLE 27-2: Detection of Primary Respiratory or Metabolic Acid–Base Disorders

Primary Disorder	pH	Pco ₂	[HCO ₃]
Metabolic acidosis	↓↓	↓	↓↓
Metabolic alkalosis	↑↑	↑	↑↑
Respiratory acidosis	↓↓	↑↑	↑
Respiratory alkalosis	↑↑	↓↓	↓

Metabolic acidosis: In primary metabolic acidosis, the body will attempt to normalize the acidemia by “blowing off” CO₂. The formula of Winters and coworkers is used to calculate the predicted Pco₂ given the [HCO₃]⁹:

$$\text{Expected Pco}_2 = 1.5 \times [\text{HCO}_3] + 8 \pm 2$$

If the measured Pco₂ is less than expected, then the patient is blowing off his or her CO₂ more than would be required to compensate for the primary metabolic acidosis, and a concomitant respiratory alkalosis is present. If the measured Pco₂ is higher than expected, then the patient is failing to blow off enough CO₂ to compensate for the primary metabolic acidosis, and a concomitant respiratory acidosis is present.

Metabolic alkalosis: In primary metabolic alkalosis, the body will attempt to normalize the alkalemia by retaining CO₂. The expected increase in Pco₂ should be approximately 0.6 times the increase in the [HCO₃]:

$$\text{Expected increase in Pco}_2 = 0.6 \times ([\text{HCO}_3] - 24) \pm 2$$

If the measured Pco₂ is less than expected, then a concomitant respiratory alkalosis is present. If the measured Pco₂ is greater than expected, then a concomitant respiratory acidosis is present. A caveat to this rule is the fact that, even in profound metabolic alkalosis, the Pco₂ will rarely rise above 50 mm Hg, which represents the upper limit of normal respiratory compensation.¹⁰ If the expected Pco₂ is greater than 50 mm Hg, failure to compensate fully is likely due to exceeding the limits of the respiratory compensatory mechanism rather than to a concomitant underlying respiratory alkalosis.

Respiratory alkalosis/acidosis: In primary respiratory acid–base disorders, the metabolic compensation for the primary disorder increases over time. Acute compensation occurs as a result of the bicarbonate buffering system, and occurs over the first 24 to 48 hours. Chronic compensation comes about as the result of the kidneys’ ability to increase or decrease production of bicarbonate and to increase bicarbonate resorption or excretion. Chronic compensatory changes are usually seen from 72 hours and beyond. The clinician must decide, based on the history and clinical presentation, how acute the primary respiratory disorder is likely to be before being able to assess the appropriateness of the metabolic compensation. Likewise, a metabolic compensation greater or less than expected may prompt a reassessment of the acuity of the primary disorder.

In *acute* primary *respiratory acidosis*, the [HCO₃] should increase by 1 mEq/L for every 10 mm Hg increase in the Pco₂. In a *chronic* primary *respiratory acidosis*, the [HCO₃] should increase by 4 mEq/L for every 10 mm Hg increase in the Pco₂.

In *acute* primary *respiratory alkalosis*, the [HCO₃] should decrease by 2 mEq/L for every 10 mm Hg decrease in the Pco₂. In a *chronic* primary *respiratory*

alkalosis, the $[\text{HCO}_3^-]$ should decrease by 5 mEq/L for every 10 mm Hg decrease in Pco_2 .

If the $[\text{HCO}_3^-]$ is lower than expected, then a concomitant metabolic acidosis may be present. If the $[\text{HCO}_3^-]$ is higher than expected, then a concomitant metabolic alkalosis may be present. It is clearly not possible for a respiratory acidosis and a respiratory alkalosis to coexist.

Step 4: Calculate the anion gap. Regardless of the primary acid–base disturbance, the anion gap (AG) should be calculated. Although the AG has limitations as a screening tool, an elevated AG should be presumed to indicate the presence of an AG acidosis. Metabolic compensation for a primary respiratory alkalosis should not elevate the AG.

Step 5: If there is a metabolic acidosis, is there another concomitant metabolic disturbance? This step is key to recognizing mixed metabolic acid–base disorders. Regardless of the primary acid–base disorder, if either Step 2 or Step 3 identified a metabolic acidosis, proceed with the following calculations:

If there is an AG metabolic acidosis (an $\text{AG} > 12$), then calculate the delta gap (Δ gap). The Δ gap is a tool that will help to reveal a concomitant metabolic alkalosis or non-AG acidosis when an AG metabolic acidosis has been found.¹¹ In a simple AG metabolic acidosis, the increase in the AG above normal should be matched millimolar for millimolar by a fall in the $[\text{HCO}_3^-]$. Let us assume the upper normal of the AG to be 12 mmol/L, and the lower normal of the $[\text{HCO}_3^-]$ to be 22 mmol/L. If we ascribe the Δ AG to be the rise in the AG above the upper limit of normal, that is,

$$\Delta \text{AG} = \text{AG} - 12$$

and the Δ $[\text{HCO}_3^-]$ to be the fall of the $[\text{HCO}_3^-]$ below normal, that is,

$$\Delta [\text{HCO}_3^-] = 22 - [\text{HCO}_3^-],$$

then the Δ gap can be calculated as follows:

$$\Delta \text{Gap} = \Delta \text{AG} - \Delta [\text{HCO}_3^-]$$

Given that in a straightforward *AG acidosis*, the rise in an AG should be perfectly matched by a fall in the $[\text{HCO}_3^-]$, we should expect a Δ gap of zero. In practice, a 2 standard deviation from the mean variation in the Δ gap would give us normal values ranging from -6 to $+6$.¹¹

If the Δ gap is less than -6 , it suggests a loss of $[\text{HCO}_3^-]$ greater than should be anticipated by the *AG acidosis* known to exist. This suggests a concomitant *non-AG acidosis*. If the Δ gap is greater than $+6$, the reduction in bicarbonate is not as great as should be expected by the known *AG acidosis*, and a concomitant *metabolic alkalosis* exists.

If there is a non-AG metabolic acidosis, then, for every unit increase in the $[\text{Cl}^-]$, there should be a unit decrease in the $[\text{HCO}_3^-]$. Remembering the discussion of electroneutrality when we looked at the AG, a decrease in the $[\text{HCO}_3^-]$

must be accompanied by an increase in the $[\text{Cl}^-]$ or in another unmeasured anion. If the increase is in an unmeasured anion, then an increase in the AG results. Since in a non-AG metabolic acidosis, we have already established a normal AG, the $[\text{Cl}^-]$ *must* increase proportional to the decrease in $[\text{HCO}_3^-]$. If we assume a normal chloride to be 100 mmol/L, then for every 1 mmol/L increase in the chloride, we should expect a 1 mmol/L decrease in the $[\text{HCO}_3^-]$, that is,

$$\text{Expected } \Delta [\text{HCO}_3^-] = \Delta [\text{Cl}^-]$$

If the measured $[\text{HCO}_3^-]$ is more than 5 mmol/L greater than expected (to allow for a 2 standard deviation range) based on the chloride concentration, then a concomitant metabolic alkalosis is present.

DIFFERENTIAL DIAGNOSIS OF ACID–BASE DISORDERS

Respiratory Acidosis

Any etiology that limits the effective minute ventilation will result in decreased ventilation and in turn an increase in Pco_2 , leading to a respiratory acidosis. A list of possible causes of respiratory acidosis is presented in Table 27-3.

Treatment of a primary respiratory acidosis should be aimed at correcting the lack of respiratory drive, reducing the effective dead space, or increasing the minute ventilation. Remember that respiratory acidosis, if not the primary acid–base disorder, may be an appropriate compensation for a metabolic alkalosis! Make sure to rule out a mixed acid–base disorder before correcting it.

Respiratory Alkalosis

Respiratory alkalosis results from excessive minute ventilation and a resultant decrease in the Pco_2 . Potential causes of a respiratory alkalosis are presented in Table 27-4. Hypocapnic patients are not always alkalemic, and a respiratory alkalosis is a common compensation for metabolic acidosis. As in a respiratory acidosis, respiratory alkalosis may be an appropriate compensation, and caution should be entertained in ascribing a respiratory alkalosis to psychogenic hyperventilation until an underlying mixed acid–base disorder has been



TABLE 27-3: Causes of Respiratory Acidosis

CNS depression
Chronic lung disease
Neuromuscular disorders
Acute airway obstruction
Pneumonia
Pulmonary edema
Thoracic cage injury
Hemothorax, pneumothorax
Pleural effusion
Mechanical ventilation



TABLE 27-4: Causes of Respiratory Alkalosis

Anxiety
Hypoxia
CNS disease
Drug use—salicylates, catecholamines
Pregnancy
Sepsis/SIRS
Hepatic encephalopathy
Mechanical ventilation

ruled out. Salicylate toxicity, in particular, can result in severe metabolic acidosis, and any treatment that removes or inhibits respiratory compensation, which can seem severe at times, may rapidly worsen the underlying acidemia.

Metabolic Alkalosis

Metabolic alkalosis is characterized by an increase in the $[\text{HCO}_3^-]$. It is brought about by the excess loss of hydrogen ions, the endogenous administration of bicarbonate or another anion such as lactate, acetate, or citrate, or, most commonly, the increased reabsorption of bicarbonate.

A *metabolic alkalosis* is classified as *chloride responsive* or *chloride resistant* based on the spot urine chloride concentration. A *chloride-responsive metabolic alkalosis* presents with a low urinary chloride concentration of less than 15 mEq/L, suggesting total body chloride depletion and, in turn, renal retention of chloride. In order to maintain electrical neutrality, low $[\text{Cl}^-]$ is accompanied by a retention of HCO_3^- ; it is this retention of HCO_3^- that brings about the resultant alkalosis. As such, chloride-responsive metabolic alkalosis is more of a problem of chloride balance than of bicarbonate balance; restoration of chloride is what is needed to allow the kidneys to normalize the $[\text{HCO}_3^-]$ and, in turn, the alkalosis. Chloride-responsive metabolic alkaloses are due to gastrointestinal losses of chloride because of gastric suctioning (direct loss of hydrochloric acid $[\text{HCl}]$), volume depletion (reduction in space of distribution of HCO_3^-), or diuretic therapy (loss of NaCl and reduction in space of distribution of HCO_3^-).¹² Chloride-responsive metabolic alkalosis is almost always associated with a volume deficit as well. Treatment should be aimed at correcting both the volume deficit and the chloride deficit, something which is most easily accomplished with normal saline (0.9% NaCl).¹³ The total deficit of chloride can be calculated according to the following equation:

$$\text{Chloride deficit (mEq)} = 0.2 \times \text{lean weight (kg)} \\ \times (\text{normal serum } [\text{Cl}^-] - \text{measured serum } [\text{Cl}^-])$$

The volume of saline, in liters to be infused, necessary to correct the chloride deficit, can then be calculated by taking the chloride deficit and dividing by 154 mEq/L (the chloride concentration of normal saline). Infusion of dilute concentrations of HCl can also be utilized to replete both hydrogen ion and chloride stores in severe cases of chloride-responsive

metabolic alkalosis, although normalization of volume status with isotonic saline is recommended first.

Chloride-resistant metabolic alkalosis is characterized by a high urinary spot chloride concentration greater than 25 mEq/L. It can be brought about by either mineralocorticoid excess or profound hypokalemia.

In a state of mineralocorticoid excess, such as Cushing's syndrome or excessive mineralocorticoid administration, the kidneys inappropriately retain HCO_3^- via an aldosterone-mediated pump in the proximal tubule. The workup should be aimed at identifying and correcting the underlying cause of the mineralocorticoid excess. Acetazolamide, by blocking carbonic anhydrase, can inhibit the reabsorption mechanism in the proximal tubule and help promote appropriate renal excretion of HCO_3^- , as well as facilitate diuresis of the fluid overload that typically accompanies this state.

Hypokalemia causes an intracellular shift of hydrogen ions, resulting—by means of a shift of the bicarbonate buffering equation to the left—in a relative excess of HCO_3^- . In this case, repletion of potassium along with volume repletion, if required, should correct the alkalemia.

In all cases of metabolic alkalosis, careful consideration should be made to the potential exogenous sources of alkali in the patient's medications and fluids. Acetate, citrate, or lactate in parenteral infusions, blood transfusions, or IV fluids should be considered. One of the most common causes of metabolic alkalosis, as mentioned later, is an inadvertent “overshoot” metabolic alkalosis that results from overly aggressive or inappropriate administration of alkali as treatment for metabolic acidosis.

See Table 27-5 for a review of the common causes of metabolic alkalosis.

Metabolic Acidosis

Metabolic acidosis is brought about due to the loss of extracellular bicarbonate (diarrhea, renal loss of bicarbonate, enterocutaneous fistulae), the accumulation of an endogenously produced organic acid (lactic acidosis, ketoacidosis), or the administration of an acid (salicylate, methanol, ethylene glycol, and so forth).

THE ANION GAP

The AG is utilized to evaluate patients with a metabolic acidosis. Metabolic acidosis can come about either due to an increase in hydrogen ion concentration or due to a loss of



TABLE 27-5: Common Causes of Metabolic Alkalosis

Chloride-Responsive Urine, $\text{Cl}^- < 15$ mEq/L	Chloride-Resistant Urine, $\text{Cl}^- > 25$ mEq/L
Vomiting or gastric suction	Mineralocorticoid excess
Diuretics	Cushing syndrome
Volume contraction	Licorice ingestion

**TABLE 27-6: Unmeasured Ions Contributing to the Normal Anion Gap**

Unmeasured Anions	Unmeasured Cations
Albumin (15 mEq/L)	Calcium (5 mEq/L)
Organic acids (5 mEq/L)	Potassium (4.5 mEq/L)
Phosphate (2 mEq/L)	Magnesium (1.5 mEq/L)
Sulfate (1 mEq/L)	
Total UA (23 mEq/L)	Total UC (11 mEq/L)

bicarbonate. The AG helps differentiate between these two possibilities.

The concept of electroneutrality dictates that the charge of all positively charged ions in the body must be matched by an equivalent charge of negatively charged ions. The AG is the difference between the total concentration of the predominant cation (Na^+) and the total concentration of the predominant anions (Cl^- , HCO_3^-):

$$\text{AG} = [\text{Na}^+] - ([\text{Cl}^-] + [\text{HCO}_3^-])$$

The value of the AG represents the normal difference between the concentrations of cations and anions not included in the AG calculation. The cations and anions that normally contribute to the AG are presented in Table 27-6. Normal values for the AG vary slightly depending on the techniques of an individual lab. The original normal range for the AG was 8–16 mEq/L, although newer laboratory techniques have resulted in a lower normal range of 3–11 mEq/L.¹⁴ This value represents the value of the relative charge superiority of unmeasured anions relative to unmeasured cations.

A metabolic acidosis that results in the accumulation of excess hydrogen ions will cause an increased AG. We will refer to this as an *AG metabolic acidosis*. This comes about because the excess hydrogen ions bind with free bicarbonate ions to form carbonic acid, driving the carbonic acid buffering equation to the right, resulting in a decreased concentration of bicarbonate:



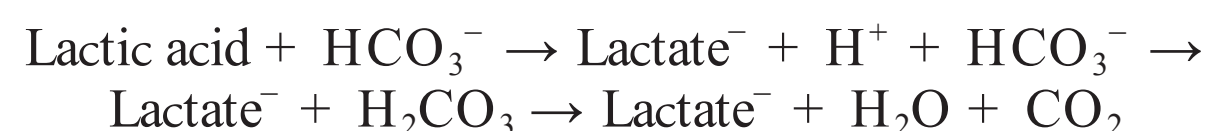
This reduced bicarbonate concentration results in a reduced measured anion concentration and, in turn, a larger AG. Caution is advised in relying too heavily on the AG as a screening measure of acidosis, especially in a clinical context when strong suspicion for organic acidosis exists. While elevated lactic acid levels should bring about a corresponding large AG, multiple studies have shown that the AG fails to predict lactate levels in both critically ill medical and trauma patients.^{15–17} In the event that an organic acidosis is strongly suspected, measuring blood levels of the organic acid directly (lactate in lactic acidosis, acetate or β -hydroxybutyrate in ketoacidosis) more reliably detects or excludes the underlying disorder.

In contrast, a metabolic acidosis that comes about as a result of a loss of bicarbonate from the extracellular fluid does not result in an increase in the AG. At first, this might seem counterintuitive. When a metabolic acidosis is brought about

by bicarbonate loss, however, the kidneys maintain electroneutrality by retaining chloride ions. Since both chloride and bicarbonate are measured anions, the total contribution of measured anion concentration to the AG remains unchanged, although the relative ratio of chloride to bicarbonate will increase. We will refer to this as a *non-AG metabolic acidosis*, although, because of the elevated relative chloride concentration, you may see *non-AG metabolic acidosis* sometimes referred to as *hyperchloremic metabolic acidosis*.¹⁸

ANION GAP METABOLIC ACIDOSIS

As mentioned earlier, an AG metabolic acidosis is brought about by the accumulation of excess hydrogen ions and the subsequent reduction in the bicarbonate concentration by means of the carbonic acid buffering system. Since the extracellular fluid must remain electrically neutral, the reduction in bicarbonate concentration must occur concurrently with an increase in another anion. The unmeasured anion that replaces bicarbonate in maintaining electrical neutrality is the conjugate base to the acid that gave off the excess hydrogen ion. In the case of lactic acidosis, lactic acid gives off its hydrogen ion, leaving behind lactate, a negatively charged ion:



Acids causing an AG metabolic acidosis can be inorganic (sulfate, phosphate), organic (lactate or ketoacids), or exogenous (salicylates). The most common causes of an AG metabolic acidosis can be remembered by the acronym A CAT MUDPILES (see Table 27-7).^{4,19} A careful history and exam combined with confirmatory tests will help narrow the differential diagnosis.

NONANION GAP METABOLIC ACIDOSIS

Non-AG metabolic acidosis is caused not by the addition or accumulation of an acid, but by the loss, through either renal

**TABLE 27-7: A CAT MUDPILES: Common Causes of Anion Gap Metabolic Acidosis and Confirmatory Tests When Appropriate**

Cause	Confirmatory Test(s)
Analgesics (NSAID, APAP)	Tylenol level, AST
Cyanide, carbon monoxide	CO level, cyanide level
Alcoholic ketoacidosis	Serum or urine ketones, ethanol level
Toluene	
Methanol, metformin	Osmolal gap
Uremia	Serum BUN, creatinine
Diabetic ketoacidosis	Serum or urine ketones, blood glucose
Paraldehyde, phenformin	
Iron, isoniazid	Serum iron level, abdominal radiographs
Lactic acidosis	Lactate or lactic acid level
Ethylene glycol	Osmolal gap
Salicylates	Salicylate level, urine ferric chloride



TABLE 27-8: HARDUP: Common Causes of Nonanion Gap Metabolic Acidosis

Hyperalimentation
Acetazolamide
Renal tubular acidosis and renal insufficiency
Diarrhea and Diuretics
Ureteroenterostomy
Pancreatic fistula

or gastrointestinal means, of bicarbonate. Causes of non-AG metabolic acidosis are shown in Table 27-8.¹⁹

The urine AG can be utilized to distinguish between renal and gastrointestinal etiologies for a non-AG metabolic acidosis.⁵ The urine anion gap (UAG) is calculated by obtaining the spot urine electrolyte values for Na, K, and Cl, as follows:

$$\text{UAG} = (\text{Urine[Na]} + \text{Urine[K]}) - \text{Urine[Cl]}$$

In the event of renal loss of HCO_3^- , the UAG would be large, as bicarbonate is not measured in the UAG and would account for a large amount of the urinary ions. In the event of gastrointestinal loss of bicarbonate, the kidneys would be retaining HCO_3^- , and the UAG would approximate zero.

TREATMENT OF ACIDOSIS WITH EXOGENOUS BICARBONATE

Bicarbonate does not function well as a buffer, in the strictest sense of the word, at near-physiologic pH.¹³ The dissociation constant or pK of the carbonic acid–bicarbonate buffering system is 6.1. If we assume that the effective range of a buffering system is within 1 pH unit of its dissociation constant (the pH level at which the acid is 50% dissociated), then the carbonic acid–bicarbonate buffering system should work effectively between a pH of 5.1 and 7.1, but would clearly not be an effective buffer at near-physiologic pH. This would be true under laboratory conditions were we simply titrating an acid. In the body, however, the respiratory system has the ability to remove CO_2 . As H_2CO_3 is formed by the buffering of excess H^+ by HCO_3^- , the subsequent increased CO_2 can be removed via increased ventilation, pulling the buffering equation to the right, and significantly extending the effective buffering range of the system.¹⁰

The administration of NaHCO_3 solutions in an attempt to increase serum pH has been a long-standing practice and one that, on the surface, would appear to make empirical sense. The principal concern for a patient in severe acidosis ($\text{pH} < 7.10$) is for impaired cardiac contractility.²⁰ Other effects of severe acidosis include centralization of blood volume, cardiac sensitization to dysrhythmias, hyperkalemia, respiratory fatigue, increased metabolic demands, insulin resistance, and obtundation or coma.²¹ Clinicians often are confronted by a desire to normalize a severely acidotic pH; the tool in our armamentarium that has been used for that purpose has been NaHCO_3 . Arguments in favor of directly correcting an acidosis with alkali therapy hinge on two presumptions: (1) correction of

the acidosis independent of addressing the underlying cause is beneficial and (2) administration of sodium bicarbonate solutions effectively corrects or improves acidosis. Neither is necessarily the case.

The administration of NaHCO_3 solutions has not been associated with decreased mortality, and can cause significant complications. In laboratory conditions, acidosis has been shown to be protective for ATP-deprived liver cells, delaying the onset of cell death.²² If we presume this to be true in vivo, then correction of acidosis without normalization of the underlying causative disorder would be harmful. The exogenous administration of NaHCO_3 also pushes the carbonic acid buffering equation to the right:



This increases the Pco_2 , increasing the respiratory burden for clearing CO_2 . In the absence of capability to increase respiratory excretion of CO_2 , the net effect of NaHCO_3 administration may be to paradoxically lower the pH due to the increased Pco_2 . In an intact organism, a severe acidemia may have already brought about a maximal respiratory effort at compensation, making the lungs unable to accommodate the increased CO_2 burden. In a patient with fixed ventilation, as on a ventilator, the administration of NaHCO_3 often produces a paradoxical acidosis as the patient is unable to accommodate the increased CO_2 burden.

The objective when treating an organic acidosis, for which an acidotic pH is almost always a marker for an underlying derangement in need of correction and not a problem itself in need of normalization, should be to correct the underlying cause of the acidosis. Restoration of tissue perfusion in lactic acidosis and of nutritional substrate in alcoholic ketoacidosis, as well as the administration of insulin in diabetic ketoacidosis, should completely correct the underlying acidosis.²³ The administration of alkali solutions to these patients concomitant with the correction of the underlying disorder almost universally causes an overshoot alkalosis.

If a severe acidosis ($\text{pH} < 7.10$) is present, the administration of alkali therapy may be required in bicarbonate-losing metabolic acidosis such as profound diarrhea or renal tubular acidosis, when the body's production of HCO_3^- cannot keep pace with losses. Alkali therapy can also provide a temporizing measure in the renal-failure patient who develops a metabolic acidosis while hemodialysis is arranged, as such a patient will be incapable of renal compensation and increased bicarbonate production or acid excretion. Alkali therapy may also be considered in the event of massive exogenous acid ingestion that exceeds the capabilities of compensatory mechanisms, such as occurs in salicylate or toxic alcohol ingestion. In this case, the additional CO_2 transport capability supplied by sodium bicarbonate may prove a temporizing measure while arranging for hemodialysis in order to remove the exogenous acid.

If the decision is made to administer sodium bicarbonate, the goal should be to partially correct a severe acidosis to no greater a pH than 7.2, to prevent a reflex alkalosis after over-correction. Inherent in the administration of sodium bicarbonate is the administration of a not insignificant amount of

sodium. While commercially produced solutions are available, in practice, an infusion is usually made by mixing 150 mEq (three standard 50-mEq ampoules) in 1 L of 5% dextrose in water (D₅W) or 100 mEq (two standard 50-mEq ampoules) in 1 L of 0.25% sodium chloride (0.25% NaCl), yielding a near-isotonic solution.²¹ The distribution of bicarbonate varies depending on the degree of acidosis, and is about 50% of lean body weight at normal pH, but increases upwards of 70% lean body weight in severe acidosis (pH < 7.10).¹⁰ If we presume to only be utilizing the administration of sodium bicarbonate in the presence of severe acidosis, and without correction upwards of a pH of 7.20, we can use 60%, or 0.6, as an estimation of the distribution of bicarbonate. Our goal should be to correct the pH to no greater than 7.20, which, according to the Henderson–Hasselbalch equation, should correspond to a [HCO₃]⁻ of 10 mmol/L. The bicarbonate deficit can be calculated according to the following equation:

$$\text{HCO}_3^- \text{ deficit (mEq)} = 0.6 \times \text{lean body weight (kg)} \times (10 - \text{measured } [\text{HCO}_3^-])$$

The total calculated deficit should be given slowly as an infusion. The net effect of the infusion will not be manifest until upwards of 30 minutes following the infusion. It is important to stress that continuing a bicarbonate infusion until normalization of pH is observed will uniformly result in an often poorly tolerated “overshoot” alkalosis. As such, only the calculated dose should be infused, with further alkali therapy directed by subsequent blood gas and electrolyte analysis.

Alternate alkali infusions have been developed that have theoretical advantages over sodium bicarbonate, including carbicarb (a 1:1 solution of sodium bicarbonate and disodium carbonate) and THAM (0.3 N tromethamine). No clinical trial has demonstrated either agent to be superior to sodium bicarbonate, and their clinical use is not indicated.^{10,23}

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Electrolyte Disorders

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INTRODUCTION

Electrolyte disorders can be some of the most complex and subtle clinical conditions facing the critical care or emergency medicine physician. A healthy degree of suspicion coupled with vigilant electrolyte monitoring is necessary in order to avoid missing these disorders. This is particularly true as many electrolyte disorders occur secondary to other severe disease states.

DISORDERS OF SODIUM

Sodium disorders are commonly encountered in clinical practice. Both hyponatremia and hypernatremia have multiple underlying causes and may develop acutely or chronically. Patients with acute or severe sodium disorders may be critically ill and require rapid, aggressive correction of their sodium abnormality, while aggressive treatment of the chronic, compensated hyponatremic or hypernatremic patient may cause dangerous fluid shifts. It is critical that the emergency physician understand how to identify, classify, and treat sodium disorders.

Hyponatremia

INTRODUCTION

Hyponatremia is defined as a serum sodium less than 135 mEq/L. It is commonly found in both inpatients and outpatients.¹ Hyponatremia is associated with increased morbidity and mortality in hospitalized patients admitted to both the medical ward and the intensive care unit.² Even mild hyponatremia in outpatients is correlated with a poor outcome.³ Groups at particular risk for hyponatremia include

hospitalized patients, elderly patients, and patients recently started on thiazide diuretics.⁴

PRESENTATION

The severity of symptoms due to hyponatremia depends on the rate of sodium decline as well as the absolute level. Mildly hyponatremic patients are often asymptomatic. Moderately hyponatremic patients (Na of 125–130 mEq/L) may experience nausea, headache, malaise, and myalgias, and have depressed tendon reflexes. Severe hyponatremia (Na < 125 mEq/L) causes mental status changes; seizure, coma, and death occur at sodium levels of below 120 mEq/L. Acute hyponatremia occurs over less than 48 hours and is likely to cause neurologic manifestations secondary to cerebral edema. In chronic hyponatremia, neurologic effects are less likely, as there has been time for compensation and brain size remains normal. This compensatory response puts the patient at risk for a demyelinating syndrome if sodium is corrected too rapidly.

EVALUATION

Evaluation of hyponatremia consists of a stepwise narrowing of the differential diagnosis based on history, physical exam, and laboratory testing^{1,5–8} (see Figure 28-1).

Hyperosmolar or Iso-Osmolar Hyponatremia

Hyponatremia in the absence of a hypoosmolar state is referred to as pseudohyponatremia. Hyperosmolar hyponatremia occurs when large amounts of an osmotically active substance (such as mannitol, glucose, or intravenous [IV] contrast dye) draw water into the vasculature and dilute sodium concentration. For pseudohyponatremia secondary

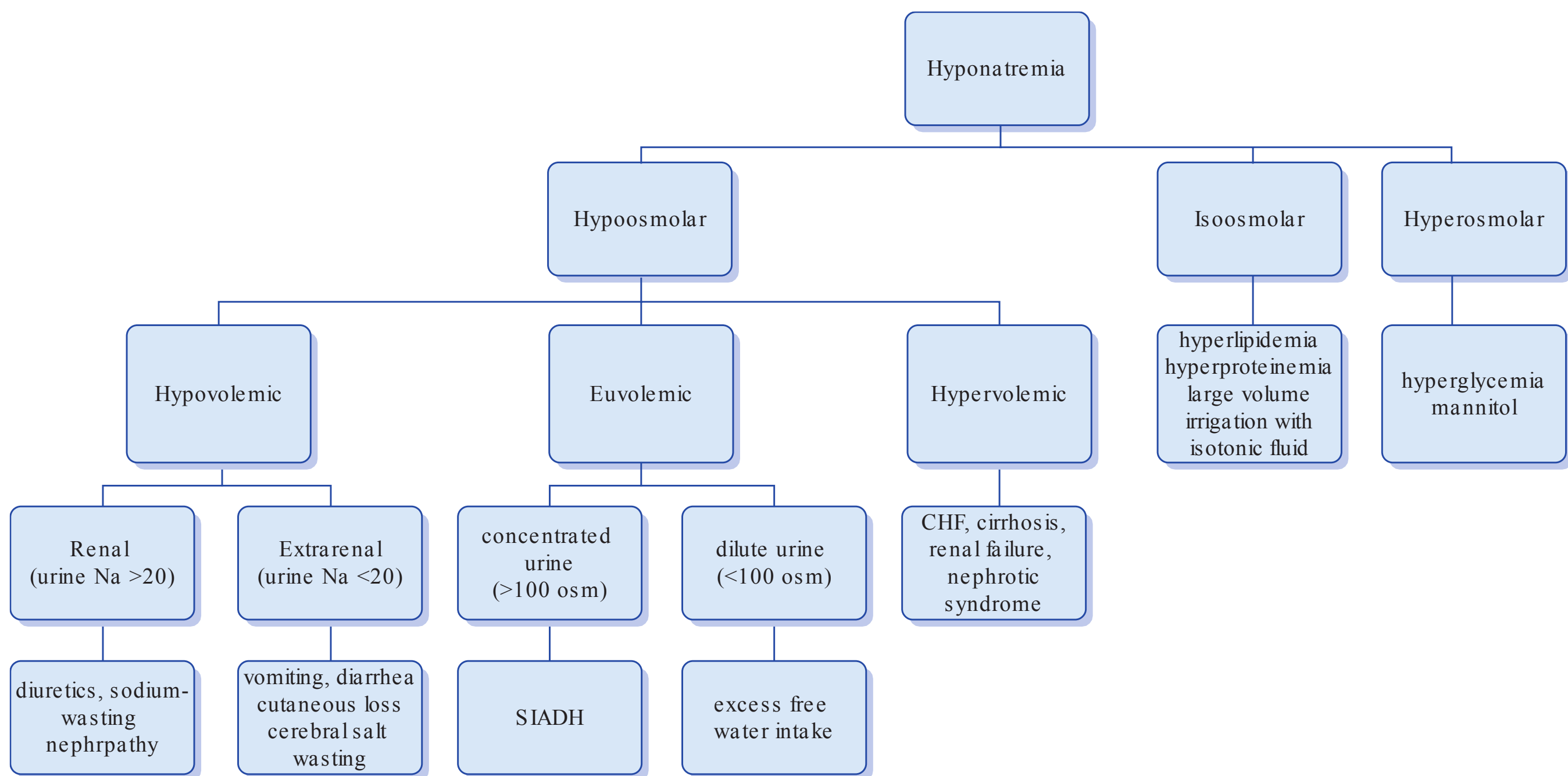


FIGURE 28-1 Etiologies of hyponatremia.

to hyperglycemia, a correction factor of 1.6 mEq/L sodium decrease for every 100 mg/dL rise in glucose is often used; however, experimental evidence indicates that a correction factor of 2.4 mEq/L may be more accurate.⁹

Iso-osmolar hyponatremia may be due to severe hyperlipidemia or hyperproteinemia, which causes a lab artifact in which serum water content is overestimated. Large-volume irrigation with a sodium-free fluid such as sorbitol, which is frequently used in transurethral prostatic resection, can cause either an iso-osmolar or hypo-osmolar hyponatremia.⁸

Hypo-Osmolar Hyponatremia

Hypo-osmolar hyponatremia is due to an excess of free water relative to solute. This may occur when water intake overwhelms the excretory capacity of the kidney or when there is an inability to suppress antidiuretic hormone (ADH) secretion secondary to true volume depletion, effective circulating volume depletion, or a primary inappropriate release of ADH.

Evaluation of the patient with hypo-osmolar hyponatremia begins with an assessment of volume status based on vital signs including orthostatics, skin turgor, mucus membranes, jugular venous distension (JVD), and presence or absence of edema and ascites. Because physical exam findings can be unreliable in assessing volume status,⁹ the patient's history, comorbidities, medications, and laboratory values should be incorporated into the assessment as well.

Hypovolemic hyponatremia occurs when sodium depletion exceeds free-water depletion. Hypovolemia prompts ADH release and thirst; thus, the patient consumes and retains free water, leading to worsened hyponatremia.

Relative sodium depletion may occur by renal or extrarenal losses of sodium and water; distinguishing between the two is based on history and measurement of urine sodium. Low urine Na (< 20 mEq/L) indicates that the kidneys are appropriately reabsorbing sodium; thus, losses are extrarenal. Causes of extrarenal loss include vomiting, diarrhea, and cutaneous loss in burn victims. Patients presenting to the ED with hyponatremia most commonly fall into this category.¹² If urine sodium is high (> 20 mEq/L), then sodium is being lost renally out of proportion to water losses. The most common cause is diuretics; the emergency physician must be particularly alert for this condition in older patients recently started on hydrochlorothiazide, as this drug is associated with a significant risk of hyponatremia.¹³ Other causes include sodium-wasting nephropathy or hypoaldosteronism.

Cerebral salt wasting syndrome (CSW) is a cause of hypovolemic hyponatremia that occurs after head injury or neurosurgical procedures. Distinguishing it from the syndrome of inappropriate antidiuretic hormone (SIADH)—which may occur in the same clinical context—is critical, as the treatment of CSW (administration of isotonic saline) may worsen SIADH. An assessment of the patient's volume status may help distinguish the two: patients with CSW are more likely to appear hypovolemic, whereas patients with SIADH are more likely to be euvolemic.⁷ In addition, CSW patients typically produce dilute urine with a high flow rate, unlike the concentrated, low-flow urine of SIADH. Spot measurement of urinary sodium cannot distinguish between these two diseases. Additional assessment of volume status, such as degree of hemoconcentration, BUN and creatinine levels, and central venous pressure (CVP), should be considered as well.¹⁴

Euvolemic hyponatremia occurs when there is free-water gain and/or retention with minimal sodium loss. SIADH is diagnosed when there is a hypo-osmolar hyponatremia with an inappropriately concentrated urine (> 100 mOsm/kg); clinical euvolemia; absence of diuretic use; and normal renal, cardiac, adrenal, and thyroid functions. It is a frequent cause of hyponatremia in hospitalized patients and may be due to malignancy, pulmonary disease, CNS disease, or drugs¹⁵ (see Table 28-1). Hypothyroidism and adrenal insufficiency may cause a similar clinical picture.

Euvolemic hyponatremia may occur in the patient with normal kidney function if the amount of free water consumed is excessive (often > 4 L per day). Etiologies include psychogenic polydipsia or beer potomania. An appropriately dilute

urine (< 100 mOsm/kg) is present as the kidney attempts to excrete free water.

Exercise-induced hyponatremia typically occurs in the setting of prolonged endurance exercise and is due to water overconsumption and/or inappropriate arginine vasopressin (AVP) secretion. Risk factors include excessive water consumption and high availability of fluids during an athletic event, female sex, lower body weight, prolonged exercise (> 4 hours) and athlete inexperience.¹⁶

Hypervolemic hyponatremia occurs in patients who are total body volume overloaded but have low effective arterial volume secondary to heart failure, cirrhosis, renal failure, or nephrotic syndrome. Hyponatremia portends a poor prognosis in heart failure patients¹⁷ and patients with cirrhosis.¹⁸



TABLE 28-1: Causes of the Syndrome of Inappropriate Antidiuretic Hormone (SIADH)

Malignancy	Lung carcinoma (small cell or mesothelioma)
	Oropharyngeal
	Gastrointestinal
	Genitourinary
	Endocrine thymoma
	Lymphoma
	Ewing's sarcoma
Pulmonary disease	Pneumonia (bacterial or viral)
	Tuberculosis
	Aspergillosis
	Asthma
	Cystic fibrosis
	Advanced chronic obstructive pulmonary disease
CNS disease	Encephalitis
	Meningitis
	Bleeding (subdural, subarachnoid, stroke)
	Intracranial mass
	Recent neurosurgical procedure
	Multiple sclerosis
	Guillain-Barré syndrome
	Cerebral sinus thrombosis
	Delirium tremens
Drugs	Acute intermittent porphyria
	Chlorpropamide
	Antidepressants
	Carbamazepine
	Nicotine
	Narcotics
	Nonsteroidal anti-inflammatory drugs (NSAIDs)
	Antineoplastic drugs
	MDMA ("ecstasy")
	AVP analogues: desmopressin, vasopressin, oxytocin
Other	Hereditary
	Idiopathic
	Transient (endurance exercise, nausea, pain, stress)

TREATMENT

Treatment of hyponatremia depends on both the etiology and the severity of the disease. Osmotic demyelination syndrome is a dreaded complication of treatment, resulting when administration of hypertonic solution causes rapid movement of water out of brain cells. Overcorrection of hyponatremia, which places patients at risk for osmotic demyelination, is common in patients presenting to the emergency department (ED).¹⁹ The emergency physician must balance the risk of overcorrection with the need to rapidly treat suspected cerebral edema.

The critically ill hyponatremic patient who presents with seizure or coma should be treated aggressively to rapidly reverse cerebral edema by correcting sodium with 4 to 6 mmol/L. Although evidence is limited, guidelines suggest administration of 100 mL of 3% saline over 10 minutes and repeated every 15 minutes $\times 2$ if needed.²⁰ Severe hyponatremic symptoms are likely to be due to a rapid fall in sodium (< 24 –48 hours) without time for the brain to compensate (such as with acute water intoxication or endurance exercise); thus, rapid correction in these patients is less likely to cause a demyelinating syndrome than rapid correction in chronically hyponatremic patients. Additionally, rate of spontaneous correction is likely to be rapid in this patient population as vasopressin secretion is appropriately suppressed. This rapid rate of correction is acceptable if the patient is known to have been hyponatremic for only a few hours; however, if patients have been hyponatremic for a longer time period, correction should be limited to 10 to 12 mEq/L over 24 hours and 18 mEq/L over 48 hours.²⁰

Classic teaching is that the stable chronically hyponatremic patient should be corrected at a rate of no more than 0.5 mEq/L/h and no more than 10–12 mEq/L/24 h⁷ to minimize risk of demyelination. However, recent reviews highlight risks of demyelinating syndromes and propose a more conservative goal of 4–8 mEq/L/d in patients at low risk of osmotic demyelination and 4 to 6 mEq/L/d in patients with high risk of demyelination (alcoholism, liver disease, hypokalemia, malnutrition, or serum sodium < 105 mEq/L).^{20–22}

The change in serum sodium estimated to result from administration of 1 L of IV fluid is calculated by the following equation:

Na change with 1 L IV fluid

$$= \frac{\text{Na content IV fluid (mEq/L)} - \text{serum Na (mEq/L)}}{\text{TBW} + 1}$$

Total body water (TBW) = correction factor \times weight (kg)

Correction factor:

Male	
Nonelderly	0.6
Elderly	0.5
Female	
Nonelderly	0.5
Elderly	0.45

The sodium content of common IV solutions is noted in Table 28-2. Serum sodium should be measured frequently (at least every 4–6 hours) during treatment, as calculations have limited accuracy and response to therapy is variable.²³ In particular, patients with a reversible cause of hyponatremia (i.e., volume depletion, cortisol deficiency, thiazide diuretics) are likely to correct rapidly once the underlying cause is removed or reversed. If correction is excessive, then it can be stopped or reversed by administering oral or IV free water or IV desmopressin.²⁰

Patients with SIADH will typically not correct and may even worsen with administration of isotonic IV fluids. For these patients, fluid restriction is recommended instead. In patients with hyponatremia related to hypothyroidism or adrenal insufficiency, treatment is directed at the underlying cause.

Conivaptan and Tolvaptan, which are vasopressin receptor antagonists, have been shown to increase serum sodium in patients with euvolemic or hypervolemic hyponatremia.²⁴ However, their use is limited in the acutely ill hyponatremic patient because a large percentage of patients do not respond and there is a high risk of overcorrection.²² Additionally, they are not recommended in treatment of hypovolemic hyponatremia or in patients with neurologic symptoms.²⁵



TABLE 28-2: Sodium Concentrations of Common IV Solutions

Solution	Sodium Concentration (mEq/L)
5% normal saline (NS)	855
3% NS	513
0.9% NS	154
Lactated Ringer's	130
0.45% NS	77
0.25% NS	38
5% dextrose in water	0
8.5% sodium bicarbonate (ampoule)	50 mEq/50 mL ampoule (1 mEq/mL)

Hypernatremia

INTRODUCTION

Hypernatremia is defined as a serum sodium > 145 mEq/L. The underlying etiology is inadequate free-water intake. This condition is rare in alert people with an intact thirst mechanism; it is more prevalent in those who rely on others for their water intake. Patients over age 60 may be particularly at risk, since the protective responses of thirst and ADH release are blunted in older age. Most outpatients who present with hypernatremia are at the extremes of age, while hospitalized patients or those with altered mental status are at risk for hypernatremia regardless of age.²⁶

PRESENTATION

Hypernatremia may present with weakness, agitation, muscle twitching, hyperreflexia, ataxia, lethargy, and coma. As with hyponatremia, symptoms in hypernatremia correlate with severity and rate of sodium change. In acute or severe hypernatremia, brain shrinkage may lead to vascular rupture with cerebral bleeding. In chronic hypernatremia, the brain adapts over time by accumulation of electrolytes; thus, neurologic symptoms may be less pronounced. However, this adaptive response complicates management because rapid correction of hypernatremia may lead to cerebral edema.²⁶

EVALUATION

As with hyponatremia, an assessment of the patient's volume status will help to clarify the etiology of hypernatremia (see Figure 28-2).

Hypovolemic hypernatremia occurs when free-water depletion exceeds sodium depletion. Similar to hypovolemic hyponatremia secondary to relative sodium depletion, relative free-water depletion may have a renal or extrarenal cause. Renal losses are due to an osmotic diuresis caused by hyperglycemia, mannitol, or a postobstructive state. In this case, free water is lost in a dilute urine (urine osmolality < 700 mOsm/kg) with concomitant renal loss of sodium (urine Na > 20 mEq/L). Extrarenal losses may be due to diarrhea, nasogastric (NG) suction, vomiting, third spacing, or skin losses as in a burn patient; urine is appropriately concentrated (> 700 mOsm/kg) and renal sodium is low (< 10 mEq/L).

Euvolemic hypernatremia is caused by free-water loss without significant sodium loss. The cause may be renal due to diabetes insipidus (DI) or extrarenal.

DI, in which the kidney does not concentrate the urine appropriately (urine osmolality < 700 mOsm/kg), will cause hypernatremia if there is insufficient access to free water. Central DI is due to decreased ADH release secondary to head trauma, neurosurgery, infiltrative disease, or an idiopathic cause. Administration of exogenous ADH will allow these patients to concentrate the urine again. In nephrogenic DI, the collecting ducts are resistant to ADH, thus, exogenous administration is ineffective. This condition is frequently drug related, with the most common causes being lithium, foscarnet, and clozapine. Other causes include

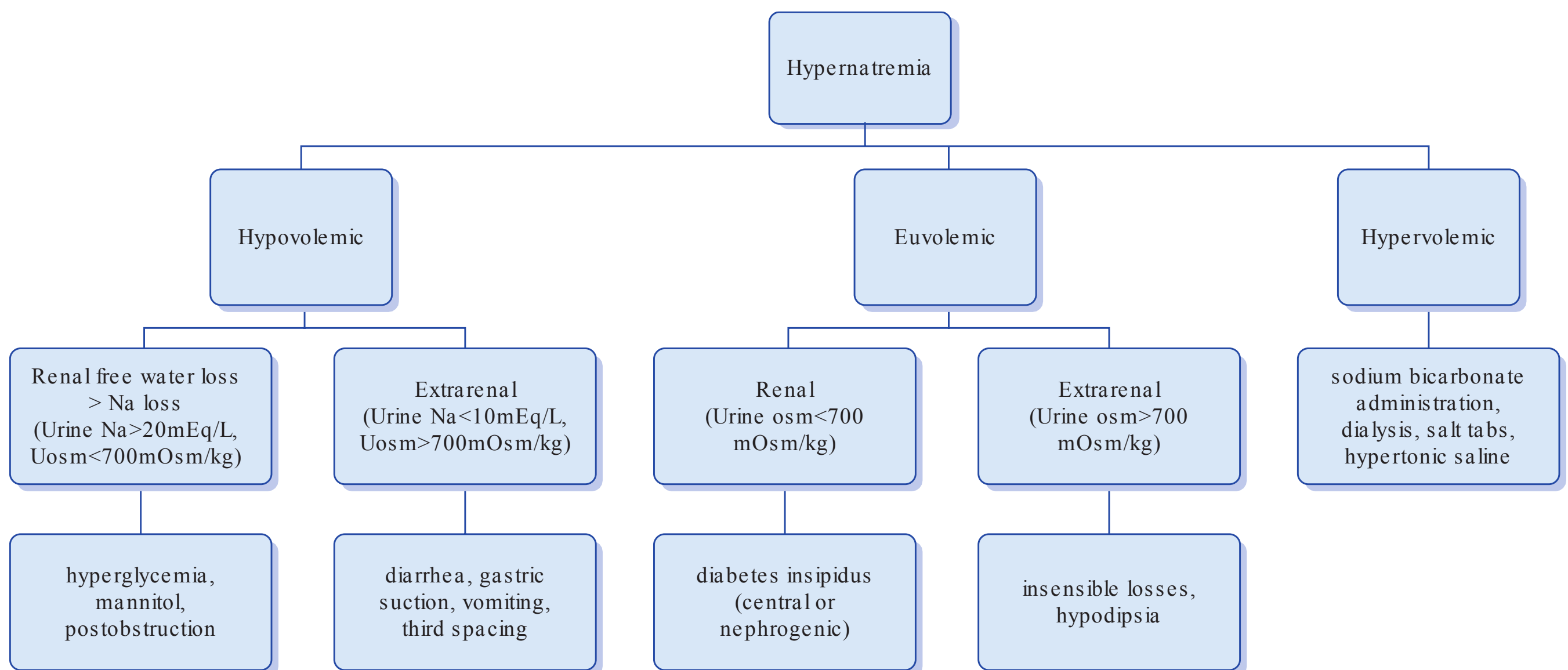


FIGURE 28-2 Etiologies of hypernatremia.

hypercalcemia, hypokalemia, low-protein diet, and release of ureteral obstruction.²⁷

Extrarenal causes include insensible losses or hypodipsia, and present with an appropriately concentrated urine (> 700 mOsm/kg).

Hypervolemic hypernatremia is caused by excessive sodium gain. It is frequently iatrogenic and may be due to excessive dosing of sodium bicarbonate, dialysis, salt tabs, or overcorrection with hypertonic saline.

TREATMENT

If the hypernatremic patient is unstable due to hypovolemia, volume resuscitation with normal saline should be aggressive until the patient is hemodynamically stable. After stabilization, fluids should be switched to 0.45% saline and correction rate monitored as described later. Although cerebral edema is a concern with rapid correction, the importance of correcting volume status outweighs the risk of this side effect. Additionally, these patients probably became hypernatremic acutely; thus, there has been less time for compensation and therefore lower risk of inducing cerebral edema. There should be a low threshold to get a head CT on the hypernatremic patient with neurologic deficit, as cerebral bleeding secondary to brain shrinkage and traction on cerebral vessels may occur.

As with hyponatremia, treatment of the stable hypernatremic patient will depend on the suspected etiology and volume status. The euvolemic patient may be treated with hypotonic saline; if central DI is suspected, vasopressin may be used. Hypervolemic hypernatremic patients require loop diuretics and free-water replacement.

The stable hypernatremic patient should be corrected gradually to minimize the risk of cerebral edema, with a goal rate of 0.5 mEq/L/h and a maximum decrease of 10 mEq/L

over a 24-hour period.¹ Expected sodium change with 1 L of fluid may be calculated by the same formula used for hyponatremia:

Na change with 1 L IV fluid

$$= \frac{\text{Na content IV fluid (mEq/L)} - \text{serum Na (mEq/L)}}{\text{TBW} + 1}$$

$$\text{TBW} = \text{correction factor} \times \text{weight (kg)}$$

Correction factor:

Male	
Nonelderly	0.6
Elderly	0.5
Female	
Nonelderly	0.5
Elderly	0.45

Total free-water deficit may be calculated by the following formula:

$$\text{H}_2\text{O deficit} = \text{calculated TBW} \times \left(\frac{\text{serum Na}}{140} - 1 \right)$$

The sodium content of common IV solutions is noted in Table 28-2. No more than half the free-water deficit should be corrected in the first 24 hours, with the remainder corrected over the next 2 to 3 days. This calculation does not account for ongoing insensible losses. As in the correction of hyponatremia, predictive calculations may not be accurate; thus, sodium should be frequently monitored. Neurologic status should be assessed frequently, as acute changes may indicate the development of cerebral edema.

DISORDERS OF POTASSIUM

Potassium disorders are the most frequently observed electrolyte disorders of hospitalized patients,²⁸ and probably of patients seen in the ED as well.²⁹ Given the predominantly intracellular distribution of potassium in the body and, in turn, the inability to truly correct serum potassium levels acutely, treatment for disorders of potassium is by necessity a protracted endeavor.

Total body potassium stores average 50 to 55 mEq/kg body weight.³⁰ Of this, approximately 98% is contained intracellularly, and about 75% of the intracellular potassium is found in muscle tissue.²⁹ The remaining 2% is extracellular, and only about 0.4% of total body potassium can be found in the plasma. The concentration of potassium in the plasma is maintained in a fairly narrow range of 3.5 to 5.0 mmol/L. The intracellular concentration of potassium averages about 150 mmol/L. The rather steep gradient of potassium across the cell membrane is maintained by the sodium–potassium ATPase pump. It is predominantly this gradient of potassium across the cell membrane that maintains resting cell-membrane potential.

Alterations in the ratio of intracellular potassium concentration to extracellular potassium concentration, $[K^+]_i/[K^+]_e$, in turn alter the resting membrane potential.³⁰ The excitability of a membrane is defined as the difference between the resting and threshold potentials. If alterations to the $[K^+]_i/[K^+]_e$ occur that increase the difference between the resting and threshold potentials, a decreased excitability is seen. Likewise, with changes in $[K^+]_i/[K^+]_e$ that decrease the difference between the resting and threshold potentials, an increased excitability is seen.

The effects of hypokalemia or hyperkalemia on resting membrane potential and, in turn, the degree to which symptoms or complications occur, are more directly related to the $[K^+]_i/[K^+]_e$ than to the serum potassium concentration. A gradual reduction in total body potassium, in which the intracellular concentration is decreased proportional to the reduction in extracellular concentration, will alter membrane excitability less than an acute change in serum potassium, in which the intracellular concentration is not allowed to equilibrate. For this reason, alterations that occur due to transcellular shift of potassium into or out of cells are more likely to manifest symptoms than those that result from gradual losses or accumulations.

Hypokalemia

Hypokalemia is defined as a serum potassium concentration of less than 3.5 mmol/L. Relatively mild hypokalemia, between 3.0 and 3.5 mmol/L, is often well tolerated by healthy people. In individuals with heart disease, particularly heart failure, even mild hypokalemia has been demonstrated to increase morbidity and mortality.^{31–33} More severe hypokalemia may be associated with generalized symptoms of fatigue, weakness, and constipation. At levels under 2.5 mmol/L, muscle necrosis can occur, and at levels less than 2.0 mmol/L, an ascending paralysis, including respiratory failure, can



TABLE 28-3: Potential Causes of Hypokalemia

Decreased potassium intake	Medications known to cause hypokalemia
Intracellular shift of potassium	Sympathomimetics
Alkalemia	Loop and thiazide diuretics
Insulin	Osmotic diuretics
Hypothermia	Carbonic anhydrase inhibitors
β -Adrenergic stimulation	Adrenocortical steroids
Increased potassium losses	Aminoglycosides
Gastric suctioning/vomiting	Amphotericin B
Diarrhea	Cation-exchange resin
Diuretics	
Hypomagnesemia	

develop. While usually not arrhythmogenic in healthy individuals, hypokalemia can induce dysrhythmias in those with underlying heart disease. Hypokalemia is well known to exacerbate the arrhythmogenic properties of digoxin.³³

Hypokalemia can arise from deficient intake of potassium, increased excretion of potassium, or a transcellular shift of extracellular potassium into cells. See Table 28-3 for a list of potential causes of hypokalemia.

The typical American diet contains a surfeit of potassium; as such, hypokalemia due to decreased intake is rare. In starvation states, or more often in critically ill patients without adequate diet repletion, it is possible to elicit a potassium-deficient state in a matter of days. Adequate repletion usually prevents this.

Low serum potassium levels can be caused by total body depletion brought about by excessive potassium losses not matched by intake. Potassium losses typically occur via either renal or gastrointestinal routes. Renal potassium losses associated with diuretic use are the most common cause of hypokalemia. Nasogastric drainage can cause hypokalemia by depleting chloride levels. Concomitant magnesium depletion exacerbates renal losses, as low magnesium levels inhibit the kidney's ability to reabsorb potassium at the distal tubule. Assessment of urinary chloride levels can help to distinguish between causes of renal potassium losses: an elevated urine chloride (> 25 mEq/L) is associated with magnesium depletion or diuretic-induced losses, while a low urine chloride (< 15 mEq/L) is associated with nasogastric drainage or alkalosis-induced potassium losses.

Gastrointestinal losses of potassium arise due to diarrhea. The potassium concentration of stool is about 75 mEq/L. In states of excessive stool volume loss, potassium losses can quickly add up.

Several factors can promote a transcellular shift of potassium from the extracellular space into the cells, leading to a low serum potassium level despite normal total body potassium stores, including hypothermia, alkalosis, and multiple medications—such as insulin and any of the sympathomimetics. Profound hypothermia may also present with immediate or delayed hyperkalemia as the result of tissue death.

Many medications induce hypokalemia. In the ED or ICU, β -agonists are the most common culprit, although their

effect at therapeutic doses is minimal, typically resulting in reductions in serum potassium levels of less than 0.5 mEq/L.³⁴ Other medications known to cause hypokalemia include loop and thiazide diuretics, osmotic diuretics, carbonic anhydrase inhibitors, adrenocortical steroids, natural penicillins, aminoglycosides, and amphotericin B.³⁵ See Table 28-3 for a list of potential causes of hypokalemia.

TREATMENT OF THE HYPOKALEMIC PATIENT

Treatment of the hypokalemic patient should begin with identification and correction of any causes for intracellular shifts of potassium. Magnesium levels should be checked and hypomagnesemia corrected prior to attempts at potassium repletion, as hypomagnesemia will preclude effective potassium repletion. If true potassium depletion is thought to exist, potential causes should be identified, beginning with a thorough review of the patient's medication profile. If causes of ongoing potassium loss can be mitigated, do so. It is often the case that treatments iatrogenically causing potassium depletion are required due to the patient's underlying disease processes. In these cases, attempts should be made to establish adequate ongoing potassium supplementation in order to prevent repeat episodes of hypokalemia. Repletion of potassium must be done relatively slowly, allowing for stable equilibration between the intracellular and extracellular compartments. Too rapid repletion of potassium will cause rapid rises in serum potassium concentrations and, in turn, acutely increase the $[K^+]_c/[K^+]_e$. IV repletion of potassium is routinely performed using potassium chloride solutions at a rate not in excess of 20 mEq/h. In cases of severe symptomatic potassium depletion, rates as high as 100 mEq/h have been reported as being used without ill effect.³⁶ Due to the irritating properties of the hyperosmotic potassium chloride solutions, infusion via a large central vein is preferred.

Oral potassium supplementation is better suited to ongoing supplementation than to rapid repletion. Oral administration has the advantage that the rate of GI absorption inherently limits rapid changes in serum potassium concentrations. Oral potassium chloride salts can be used, or, in the context of concomitant hypophosphatemia, potassium phosphate salts.

Given the difficulty in estimating total body potassium deficit from the serum potassium level, it should come as no surprise that estimating the total amount of repletion required is difficult at best. In addition, the serum concentration to total body potassium stores relationship is not a linear one. Ongoing losses of potassium during attempts at repletion make calculating total repletion doses required more difficult. Due to the large intracellular distribution of potassium and the necessity of slow repletion, several days of repletion are often necessary in order to normalize serum concentrations safely. The best way to track the amount of repletion required is to monitor repeated serum potassium concentrations. Due to the nonlinear nature of the serum potassium concentration to total body potassium levels, early repletion is likely to have minimal effects on serum concentration while smaller amounts of repletion will have more dramatic effects



TABLE 28-4: Potential Causes of Hyperkalemia

Decreased potassium excretion	Medications known to cause hyperkalemia
Renal failure	Citrate
Type IV renal tubular acidosis	Penicillin G
Hypoaldosteronism	Spironolactone/amilofide
Extracellular shift of potassium	Triamterene
Acidemia	Trimethoprim
β -Adrenergic blockade	β -Blockers
Hyperkalemic periodic paralysis	Digoxin
Drug induced	Angiotensin-converting enzyme inhibitors
Loss of cellular integrity	Angiotensin receptor blockers
Hemolysis	Succinylcholine
Ischemia	Heparin
Necrosis	

on serum concentration as the patient's total body potassium concentrations approach normal. As a general rule, however, a total of 175 mEq of potassium, given over several doses, should be needed for every 0.5 mEq/L decrease in the serum potassium level.³⁷

Hyperkalemia

Elevated serum potassium levels are potentially arrhythmogenic due to their destabilizing effect on the myocardial cell membrane. See Table 28-4 for a list of potential causes of hyperkalemia.

Hyperkalemia may be due to inability to excrete excess potassium, as occurs in renal failure, or due to a release of intracellular potassium into the extracellular space. Release of intracellular potassium stores can occur either as a result of a transcellular shift, as mentioned earlier, or as a result of cell ischemia and necrosis. Acutely ischemic skeletal muscle or gut, given the high concentration of potassium in muscle cells, can cause dramatic releases of potassium. Complications due to the rapid development of hyperkalemia following reperfusion of ischemic tissue are often cited as a proximate cause of death following crush injury. Hyperkalemia is rarely caused by excessive intake, except when associated with renal failure. The effects of hyperkalemia can be seen transiently if too rapid repletion of potassium is undertaken, without allowing time for the extracellular and intracellular compartments to equilibrate. Multiple medications can induce hyperkalemia, including cation-exchange resins, citrate, spironolactone/amilofide, triamterene, trimethoprim, digoxin, angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, heparin, and succinylcholine.³⁵ See Table 28-4 for a list of potential causes of hyperkalemia.

The immediate concern following the identification of hyperkalemia is the need to stabilize myocardial cell membranes in order to prevent arrhythmic complications. A 12-lead EKG should be obtained, and examined for evidence of cell membrane instability. EKG abnormalities associated with mild hyperkalemia include large-amplitude T waves,

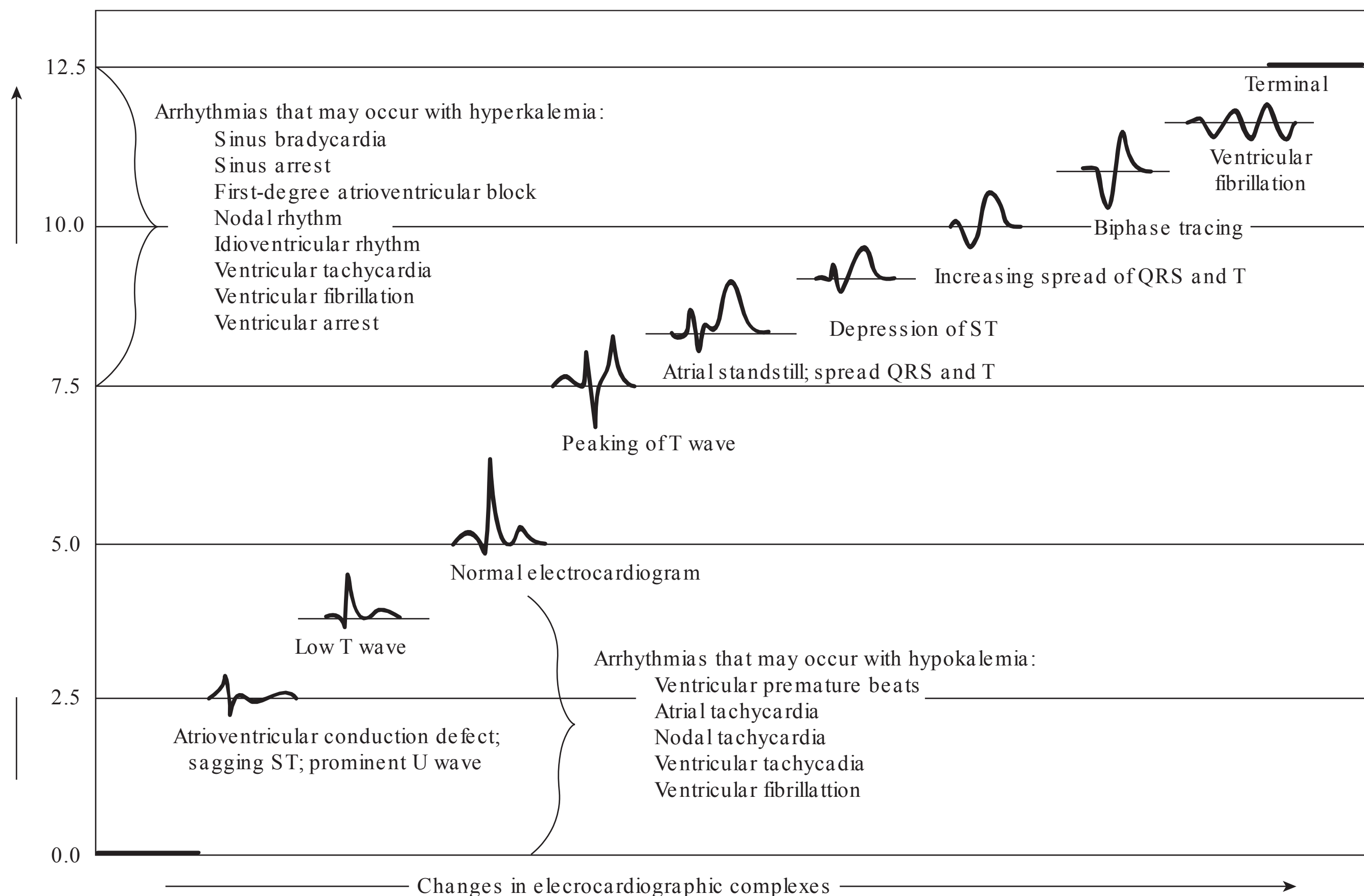


FIGURE 28-3 Correlation between serum potassium concentration and EKG findings. (Reproduced with permission from Stone CK, Humphries RL: *Current Diagnosis and Treatment: Emergency Medicine*, 6th edition. New York: McGraw-Hill, Inc; 2008.)

and “peaked” or “tented” T waves. Moderate hyperkalemia can result in PR interval prolongation, decreased P-wave amplitude or disappearance, QRS complex widening, and conduction blocks with escape beats. Severe hyperkalemia can result in a sine-wave pattern, ventricular fibrillation, and eventually asystole³⁸ (see Figure 28-3).

If hyperkalemia has produced electrocardiographic evidence of myocardial instability, administration of calcium-containing salt solution should be undertaken immediately, as calcium will help stabilize the myocardial membrane while subsequent efforts are made to normalize the serum potassium concentrations. Calcium is commonly available in calcium chloride and calcium gluconate solutions. Calcium chloride should only be infused via a large central line, as it is very hyperosmolar. Administration of 10 mL of 10% calcium chloride or 30 mL of 10% calcium gluconate will have effects within minutes, but those effects will only last 30 to 60 minutes, requiring that other acute interventions be undertaken in that interval.

Treatments for hyperkalemia can be divided into those that temporize the hyperkalemia by inducing an intracellular shift of potassium and those that remove total body potassium. The former may be more appropriate if the hyperkalemia is suspected to be due to transcellular shifts of potassium as opposed to a total body excess of potassium.

Aggressive hydration with isotonic normal saline IV solution will help dilute the serum potassium, as well as promote diuresis and renal excretion of potassium if the patient is not oliguric. In the context of ischemia, aggressive resuscitation will help minimize ongoing potassium release by restoring perfusion.

Sodium bicarbonate induces an intracellular shift of potassium by inducing relative alkalemia. Because sodium bicarbonate and calcium salt solutions can precipitate when coadministered, some authors have advocated not using sodium bicarbonate if calcium salt administration is being performed. The risks of coadministration of sodium bicarbonate and calcium salts can be minimized by administering them through separate IV lines and/or temporally spacing their respective administration if the advantages of sodium bicarbonate administration are felt to be warranted.

β -Agonists cause an intracellular shift of potassium. Because β -agonists have arrhythmogenic properties of their own, some caution may be advised in their utilization, particularly in the presence of hyperkalemic EKG changes. The use of β_2 -specific agonists, albuterol in particular, can lower the serum potassium concentration acutely.

Insulin causes an intracellular shift of potassium. Because of insulin’s obvious effect on serum blood sugars, it usually requires the coadministration of a dextrose-containing

solution to prevent hypoglycemia. Typical dosing is 10 U of regular insulin administered with one or two ampoules of 50% dextrose in water (25–50 g D50).

Sodium polystyrene sulfonate (SPS) is a gastrointestinal-binding resin that exchanges sodium cations for potassium cations in the intestinal lumen, resulting in the fecal excretion of potassium. It does not work acutely, as it requires the progressive equilibration of potassium across the intestinal mucosa. Effects are usually seen within 4 to 6 hours. Faster onset may be seen with the use of a retention enema of SPS. It is used more typically in the chronic renal failure patient in order to help prevent hyperkalemia. When initiated early in the acutely hyperkalemic patient, SPS may help prevent later rebound hyperkalemia after the effect of other acute interventions has begun to wane.

Diuretics are a frequent cause of hypokalemia; thus, it should be no surprise that they are employed to counter hyperkalemia. Nonpotassium-sparing diuretics, most commonly furosemide, induce renal excretion of potassium. When using diuretics to remove excess potassium, replace urinary fluid output with isotonic IV fluid.

Hemodialysis will acutely clear elevated serum potassium levels as well as normalize hyperkalemia-inducing metabolic acidosis, and is the treatment of choice for acute severe hyperkalemia. The rate of clearance will vary depending on the dosing of dialysis and the dialysate chosen. Patient's electrolytes should be monitored closely following hemodialysis, as rebound hyperkalemia often occurs as the intracellular and extracellular compartments reequilibrate. Repeat runs of hemodialysis or a steady state of continuous renal replacement therapy may be required. As the initiation of hemodialysis often requires a significant amount of time, even in the well-resourced facilities, its availability should not preclude the early application of other more immediately available interventions.

DISORDERS OF MAGNESIUM

Magnesium is the second most prevalent intracellular cation, next to potassium. It serves as a cofactor for enzymatic reactions involving adenosine triphosphate (ATP), including the sodium–potassium ATPase pump responsible for maintaining cell membrane potential. Magnesium also regulates the transport of calcium into smooth muscle cells.

Total body magnesium stores are approximately 24 g in the adult. Only about 1% of this is located in the extracellular fluid compartment, making imputation of the total body magnesium status from serum measures very difficult.³⁹

Magnesium Deficiency

EFFECTS OF MAGNESIUM DEFICIENCY

There are no characteristic clinical findings specific for magnesium deficiency. Hypokalemia and/or hypocalcemia suggest the possibility of magnesium depletion, as low magnesium levels will impair renal absorption of potassium and the secretion of parathyroid hormone (PTH), respectively.

Cardiac dysrhythmias are associated with magnesium depletion, as magnesium is a cofactor in the sodium–potassium ATPase pump. Depletion of magnesium can result in depolarized myocytes and predispose to tachydysrhythmias. Magnesium depletion will accentuate the effects of digitalis toxicity, as both agents have their effect on the sodium–potassium ATPase membrane pump.⁴⁰ This is of particular concern, as patients on digitalis are often also prescribed diuretics. Magnesium deficiency is associated classically with torsades de pointes, for which the rapid administration of magnesium is a first-line therapy.

Magnesium's effect on smooth muscle has led to its use as an adjunctive therapy in severe asthma, although to what degree magnesium depletion might be contributory to the exacerbation of that disease state is unclear.

CAUSES OF MAGNESIUM DEFICIENCY

Like potassium, low magnesium levels may be due to intracellular shifts of magnesium, or due to renal or gastrointestinal losses. Nonpotassium-sparing diuretics—in particular, the loop diuretics—impair magnesium reabsorption and result in renal losses. Lower GI losses due to diarrhea result in loss of magnesium in the stool. Unlike potassium, however, upper GI losses due to vomiting or gastric drainage rarely lead to significant magnesium losses. Drug-induced causes of renal magnesium loss other than diuretics include use of aminoglycosides, amphotericin, pentamidine, cisplatin, and cyclosporine.³⁵ Digitalis, insulin, and epinephrine can all cause intracellular shifts in magnesium. Absent excessive losses, low magnesium levels are not frequently due to poor dietary intake in developed countries. An exception to this has been in the alcoholic population, in which magnesium deficiency due to poor diet may impair attempts at thiamine repletion, as magnesium is a cofactor in the metabolism of thiamine into thiamine pyrophosphate.⁴¹ See Table 28-5 for a list of potential causes of magnesium deficiency.

DIAGNOSIS OF MAGNESIUM DEFICIENCY

To even a greater degree than with potassium, the serum magnesium level is a poor measure of total body magnesium



TABLE 28-5: Potential Causes of Magnesium Deficiency

Gastrointestinal losses	Medications known to cause magnesium deficiency
Diarrhea	Aminoglycosides
Renal losses	Amphotericin B
Medication induced	Cisplatin
Alcoholism	Cyclosporine
Hypercalcemia	Digoxin
	Diuretics
	Ticarcillin
	Foscarnet
	Methotrexate

stores. The majority of magnesium is intracellular or within bone, and of the extracellular magnesium, much is protein bound and inert. Serum magnesium levels do not distinguish between ionized and bound forms of magnesium and, unlike calcium, specific ionized magnesium assays are not routinely available in most labs.⁴²

Low serum levels of magnesium almost always reflect deficiency and warrant repletion, but many patients with deficiencies of magnesium have normal levels of serum magnesium. In the absence of renal disease or of renal losses of magnesium, the urine magnesium level may be a useful measure.

Often, the only indication that magnesium may need repletion is the clinical suspicion brought about by identifying a predisposing condition. Patients on loop diuretics, those with refractory hypokalemia or hypocalcemia, anyone with an osmotic diuresis, those with lower GI losses due to diarrhea, and alcoholics undergoing thiamine repletion may all warrant repletion of magnesium based on clinical suspicion alone, regardless of otherwise normal serum magnesium levels.

TREATMENT OF MAGNESIUM DEFICIENCY

Repletion of magnesium, as with potassium, must be done over time, although for different reasons. Once magnesium is infused, the shift from extracellular to intracellular fluid compartment is gradual, and renal excretion of perceived excess magnesium begins almost immediately after infusion. As such, a single dose of IV magnesium is likely to have an effect on serum concentrations for only about 30 minutes unless followed up by a steady-state administration over time while intracellular stores are repleted. Oral magnesium agents are useful in the outpatient environment to supplement diet and prevent deficits due to diuretic use, but are rarely adequate to replete deficits in the acute setting.

The IV solution of 50% magnesium sulfate (MgSO_4) is the agent most commonly available. This solution contains 4 mEq/mL of elemental magnesium. The 50% MgSO_4 solution is very hyperosmolar (4,000 mOsm/L), and should be diluted 5:1 to a 10% solution in normal saline before infusing.

Magnesium-depleted patients should be treated differently based on the severity of their depletion.^{42,43} For mild asymptomatic hypomagnesemias, assume a total magnesium deficit of 1 to 2 mEq/kg. Because approximately 50% of the repleted magnesium will be lost in urine before intracellular equilibration, replete twice the anticipated deficit. Administer 1 mEq/kg over the first 24 hours, then 0.5 mEq/kg per day over the next 3 to 4 days. If enteral access exists, oral repletion may be appropriate.

For moderate hypomagnesemia (< 1 mEq/L), add 6 g of MgSO_4 to 250 mL of normal saline and infuse over 3 hours, then 5 g of MgSO_4 in 250 mL of normal saline over the next 6 hours, and finally 5 g of MgSO_4 every 12 hours for the next 5 days.

For severe life-threatening hypomagnesemia, or repletion in the context of torsades de points or seizure activity, infuse 2 g of MgSO_4 IV over 2 to 5 minutes. This dose may be repeated. Follow this with 5 g MgSO_4 in 250 mL of normal

saline over the next 6 hours, then an additional 5 g of MgSO_4 every 12 hours for 5 days.

Magnesium Excess

Elevated magnesium levels are rarely a problem outside the context of renal failure, as excess magnesium is excreted renally with great facility. Symptomatically, hyporeflexia is seen at serum levels around 4 mEq/L, first-degree AV block at levels around 5 mEq/L, complete heart block at levels around 10 mEq/L, and cardiac arrest at levels around 13 mEq/L.⁴⁴ It would be rare to achieve clinically problematic elevated levels of magnesium in the context of renal failure without first encountering clinically significant hyperkalemia, unless an untoward level of magnesium intake were being undertaken. Hemodialysis is the treatment of choice for malignant hypermagnesemia. The administration of calcium salts, either calcium chloride or gluconate, can be used to temporize the conduction delays due to excess magnesium while hemodialysis is arranged.

DISORDERS OF CALCIUM

Calcium is the most abundant electrolyte in the human body, but the vast majority of it (99%) is found in bone. The portion of calcium in the serum, which is measured on routine calcium concentration assays, exists partially as albumin or other protein-bound calcium, partially as chelated calcium, and partially as ionized calcium. Only the ionized calcium is metabolically active and of interest clinically. Unfortunately, routine lab values fail to distinguish between the different forms of serum calcium. Since variations in albumin concentration, as well as variations in the degree of calcium binding to albumin, directly affect the ionized calcium proportion, attempts at imputing the ionized calcium level from the total serum level of calcium are difficult at best. A number of calculations have been proposed to adjust the serum calcium concentration based on the serum albumin concentration; none reliably work in the acutely ill patient.⁴⁵ The only way to meaningfully appreciate the concentration of active ionized calcium is to directly measure the ionized calcium with an ion-specific probe. Fortunately, direct serum measurement of ionized calcium levels can now be routinely performed in most labs in a timely fashion. Normal values for serum ionized calcium are between 1.1 and 1.3 mmol/L (4.5–5.0 mg/dL).

Hypocalcemia

EFFECTS OF HYPOCALCEMIA

Hypocalcemia induces increased excitability of muscle tissue, leading to cardiac irritability and muscle twitching (evidenced by the oft-referenced, but not sensitive, Chvostek and Trousseau signs). Ionized hypocalcemia also impairs strength in muscle contractions, due to calcium's role in actin/myosin chain interactions. The result is progressive twitching, leading eventually to tetany of skeletal muscles and hyperreflexia. Tetany of the laryngeal muscles may occur, creating an airway



TABLE 28-6: Potential Causes of Ionized Hypocalcemia

Nonmedication induced

Hypoparathyroidism
 Vitamin D deficiency
 Chronic renal failure
 Pancreatitis
 Citrate excess
 Tumor lysis syndrome
 Hyperphosphatemia
 Hypomagnesemia
 Sepsis/systemic inflammatory response syndrome

Medication induced

Fluoride poisoning
 Bisphosphonates
 Calcitonin
 Amphotericin B
 Cimetidine
 Phenytoin
 Ketoconazole
 Primidone
 Aminoglycosides
 Phenobarbitol
 Heparin
 Chemotherapeutic agents
 Loop diuretics
 Isoniazid

emergency. Cardiovascular effects include increased excitability and ectopy along with decreased myocardial function.

CAUSES OF HYPOCALCEMIA

Hypocalcemia is often seen in the acutely ill patient. While disorders of parathyroid function are the most common causes of hypocalcemia in the outpatient, they are rarely the culprit in the critically ill patient. Hypocalcemia in the critically ill patient is often multifactorial. See Table 28-6 for a list of potential causes of ionized hypocalcemia.

Medications that can induce hypocalcemia include fluoride poisoning, bisphosphonates, calcitonin, amphotericin B, cimetidine, ethanol, foscarnet, citrate, albumin, heparin, phenytoin, rifampin, aminoglycosides, loop diuretics, isoniazid, and propothiouracil.³⁵

Hypomagnesemia can blunt calcitriol production as well as blunt the end-organ response to calcitriol. For this reason, repletion of magnesium in the case of low magnesium levels or refractory ionized hypocalcemia is recommended. Hyperphosphatemia can lead to chelation of ionized calcium in renal failure. Chelation of ionized calcium also occurs during massive blood transfusions, in which large cumulative infused amounts of citrate (used as anticoagulant in stored blood products) can drop the ionized calcium levels. For this reason, monitoring and repletion of ionized calcium should be performed as necessary during massive transfusions, particularly in the context of refractory hypotension.⁴⁶

Sepsis and the systemic inflammatory response syndrome (SIRS) are associated with hypocalcemia, probably due to decreased PTH and calcitriol production.⁴⁷ No clinical benefit has been seen with ionized calcium repletion in sepsis if patients are asymptomatic, and it is not clear if sepsis-related ionized hypocalcemia is protective or deleterious.

TREATMENT OF HYPOCALCEMIA

Treatment of ionized hypocalcemia is 2-fold: (1) identify and treat the underlying disorder that gave rise to the ionized hypocalcemia; and (2) replete symptomatic or severe (< 0.8 mmol/L) ionized hypocalcemia emergently. Calcium requires urgent repletion only if symptomatic or if approaching critically low levels. Previous studies have suggested no advantage to repletion of asymptomatic ionized hypocalcemia

above levels of 0.65 mmol/L,⁴⁸ while one recent study indicated increased adverse outcomes only in patients with ionized calcium levels below 0.8 mmol/L.⁴⁹ Calcium administration is not benign, particularly in the context of tissue hypoxia, in which calcium administration can aggravate cellular injury.⁵⁰ Rapid infusion of calcium solutions can cause bradycardia, hypotension, and vasodilatation. When indicated, IV repletion should be undertaken with either calcium gluconate or calcium chloride. Both calcium gluconate and calcium chloride come in 10-mL vials, each containing 100 mg of its respective compound. Calcium chloride, however, has three times the elemental calcium of calcium gluconate (27 mg/mL [1.36 mEq/mL] vs. 9 mg/mL [0.46 mEq/mL], respectively). Calcium chloride is significantly more hyperosmolar than calcium gluconate ($2,000$ mOsm/L vs. 680 mOsm/L), thus should be infused only through a large central line. Both solutions should be diluted in normal saline or dextrose 5% in water prior to administration. Calcium will equilibrate between the extracellular and intracellular space following infusion; the immediate results seen following infusion will wane within 30 minutes of administration unless a follow-up infusion is started.⁴⁸ A total of 200 mg of elemental calcium (corresponding to approximately 8 mL of 10% calcium chloride, or 22 mL of 10% calcium gluconate) may be required to increase the ionized calcium 0.1 mmol/L.

Hypercalcemia

Hypercalcemia, defined as an increase in ionized calcium greater than 2.6 mmol/L, is rare in critically ill patients. The most common cause of hypercalcemia in the ED, as in outpatients, is primary hyperparathyroidism, which can be diagnosed with a PTH level. When present in critically ill patients, hypercalcemia is most often associated with underlying malignancy, although it may also be seen in other disorders that result in increased bone resorption such as sarcoidosis or with prolonged immobilization. A few medications can cause hypercalcemia, including thiazide diuretics, lithium, and vitamin D or A supplementation.³⁵

EFFECTS OF HYPERCALCEMIA

Mild hypercalcemia is often asymptomatic. Gastrointestinal symptoms include ileus, constipation, nausea, and vomiting

due to smooth muscle relaxation. Patients often suffer from severe lethargy, dehydration due to polyuria, and stupor. Cardiac features include shortened QTc, broadened T waves, and first-degree AV block. There is very poor correlation between serum calcium levels and the severity of symptoms.⁵¹

TREATMENT OF HYPERCALCEMIA

IV fluid hydration and diuresis to promote renal excretion are indicated if the patient is symptomatic or, in the case of ionized calcium levels, greater than 3.5 mmol/L.⁵² If underlying malignancy is suspected, use of salmon calcitonin or bisphosphonates may be useful. Hydrocortisone may be useful in the case of multiple myeloma.⁵³

DISORDERS OF PHOSPHORUS

Phosphorus (PO_4) exists predominantly in bone, and as free ionic PO_4 intracellularly. PO_4 is critical in all ATP-related energy-requiring cellular activities such as glycolysis and high-energy phosphate bond formation. Normal serum levels of PO_4 are 2.5 to 5.0 mg/dL, or 0.8 to 1.6 mmol/L.

Hypophosphatemia

Hypophosphatemia can be the result of an intracellular shift of PO_4 , an excess of PO_4 secretion, or a deficiency in PO_4 intake.

EFFECTS OF HYPOPHOSPHATEMIA

Hypophosphatemia is usually clinically silent unless very profound. The effects of hypophosphatemia are all related to cellular energy production, including a decrease in cardiac output observed in heart failure patients, a theoretical decrease in skeletal muscle strength, and reports of difficulty weaning from ventilators due to respiratory muscle weakness.^{54,55} Multiple reports of cardiac arrest, cardiovascular collapse, or profound encephalopathy associated with profound hypophosphatemia exist in the emergency medicine literature, many associated with intracellular shifts of PO_4 during high-dose insulin therapy for DKA.^{56–58}

CAUSES OF HYPOPHOSPHATEMIA

The transit of glucose into cells is an active process in which PO_4 is cotransported into the cell. As such, both the feeding of a patient who has been nutritionally deprived and the aggressive use of insulin for tight euglycemic control can cause dramatic intracellular shifts of glucose and, in turn, PO_4 . Any time that nutritional support is started on a patient after a period of deprivation, gradual increases in caloric intake along with frequent assessment of serum PO_4 levels should be undertaken.

Alkalosis can cause intracellular shift of PO_4 , presumably due to increased glycolysis that accompanies increased intracellular pH. This is seen to a far greater degree in respiratory alkalosis than in metabolic alkalosis, and accounts for



TABLE 28-7: Potential Causes of Hypophosphatemia

Internal redistribution	Medications known to cause hypophosphatemia
Refeeding syndrome	Antacids
Respiratory alkalosis	Sucralfate
Sepsis/systemic inflammatory response syndrome	Phosphate binders
Decreased intestinal absorption	Aspirin (in overdose)
Inadequate dietary intake	Catecholamines
Chronic diarrhea	Acetaminophen (in overdose)
Increased urinary losses	Glucocorticoids
Hyperglycemia	Diuretics
Osmotic diuresis	Theophylline (in overdose)

the increased incidence of hypophosphatemia seen in chronic obstructive pulmonary disease (COPD) patients.⁵⁹

The use of β -receptor sympathomimetics is associated with a transient intracellular shift of PO_4 , although the clinical significance of this is not clear.⁶⁰ The same response to sympathetic tone may account for the hypophosphatemia seen in sepsis or SIRS.

The use of antacid compounds, such as sucralfate or aluminum hydroxide, can bind phosphate in the upper gastrointestinal tract and impair its absorption.

Other medications that can cause hypophosphatemia include glucocorticoids, insulin, and, when in overdose, acetaminophen, aspirin, and theophylline.³⁵

Osmotic diuresis, as a result of either hyperglycemia or administration of an osmotic diuretic, can impair renal reabsorption and lead to urinary wasting of phosphate.

See Table 28-7 for a list of potential causes of hypophosphatemia.

TREATMENT OF HYPOPHOSPHATEMIA

PO_4 can be repleted in IV formulation with either sodium phosphate (93 mg/mL [3 mmol/mL] PO_4 , 4.0 mEq/mL sodium) or potassium phosphate (93 mg/mL [3 mmol/mL] PO_4 , 4.4 mEq/mL potassium). Patients presenting with a serum PO_4 of less than 2.0 mg/dL should receive 15 mmol of sodium phosphate in 100 mL of sodium chloride, infused over 2 hours. If a concomitant hypokalemia exists, potassium phosphate can be substituted at an equal dose. If follow-up serum PO_4 levels at 6 hours remain less than 2 mg/dL, identical repeat doses can be administered up to 45 mmol of PO_4 in a 24-hour period.⁶¹ If no central venous access is available, these doses should be diluted in a total of 250 mL of normal saline in order to prevent phlebotic complications of infusing a hyperosmolar solution. Oral PO_4 -containing solutions, such as K-Phos or Neutra-Phos, cannot be used effectively for the large doses of PO_4 required to replete severe hypophosphatemia (< 1.0 mg/dL), as they tend to promote diarrhea, but can be used to maintain PO_4 levels once repletion via IV is complete, or to replete mild asymptomatic phosphate deficits.⁶² Repletion of mild to moderate hypophosphatemia in the ED may be accomplished with the administration of

2 to 3 g of sodium phosphate or potassium phosphate, most formulations of which contain 8 mmol of PO_4 per packet or capsule. Daily PO_4 intake requirements, absent excessive losses, are about 1,200 mg (38 mmol) per day orally or about 800 mg (25 mmol) per day IV for a 70-kg adult.

Hyperphosphatemia

Hyperphosphatemia occurs as the result of renal failure or the widespread necrosis of cells, as in ischemia/reperfusion, rhabdomyolysis, or tumor lysis. The principal concern is for the formation of calcium- PO_4 insoluble complexes and subsequent profound hypocalcemia. Treatment is with IV hydration, and the administration of PO_4 -binding agents via the gastrointestinal tract, such as sucralfate, aluminum-containing antacids, or calcium acetate. Hemodialysis, while rarely necessary, may be employed to promote PO_4 clearance in the renal failure patient.⁵⁵

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Acute Kidney Injury

Kimberly A. Boswell • Jay A. Menaker

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INTRODUCTION

Acute kidney injury (AKI), formally known as acute renal failure (ARF), is a well-established entity in the critically ill and has long been studied. It is categorized by a sudden decrease in a patient's glomerular filtration rate (GFR), which ultimately leads to the body's inability to maintain fluid, electrolyte, and toxin homeostasis. There are many etiologies, of which the most frequent and applicable to the emergency medicine physician will be described in this chapter. Regardless of the etiology, every diagnosis can be placed among one of three categories, including prerenal, intrinsic renal, or postrenal causes. The frequency of various etiologies is largely dependent on the patient. Hospitalized patients more often have intrinsic renal disease (most commonly acute tubular necrosis) due to sepsis, ischemia, or exposure to nephrotoxic medications or substances.¹ Patients presenting to the emergency department (ED) are more likely to have pre- and postrenal causes in addition to intrinsic glomerular disease etiologies such as nephritic or nephrotic patterns.

AKI carries an associated increase in both acute morbidity and mortality within the critically ill population, but also has impacts on hospital length of stay (LOS), long-term morbidity, and mortality risks from several different etiologies.

DEFINITION

AKI was previously termed ARF in critically ill patients, and had been described using many different definitions. In 2004, Bellomo et al., as a part of the Acute Dialysis Quality Initiative (ADQI) set forward to establish a single definition of AKI in addition to evaluating the literature to offer

a cohesive recommendation for the use of fluid management and endpoint goals in AKI. The result of their evaluation was the creation of the RIFLE Criteria, a classification system commonly used today to describe AKI² (Figure 29-1). Each sequential letter of the acronym describes an increased degree of renal impairment based on either GFR or urine output. The term ARF now applies to the most severe degree of AKI, which requires the intervention of renal replacement therapy. Since inception, the RIFLE Criteria have been studied and correlated with prognosis in the intensive care unit (ICU).³⁻⁵ The RIFLE Criteria have been scrutinized and modified by several organizations, including the Acute Kidney Injury Network (AKIN) and the Kidney Disease/Improving Global Outcomes (KDIGO). Overall, however, only small alterations have been made to the original RIFLE Criteria, all of which ultimately still use serum creatinine and urine output as measures of renal injury.⁶⁻⁷

In most settings, monitoring the GFR and creatinine are more reliable ways of assessing changes in renal function. However, in the ED, baseline creatinine is often unknown; thus, urine output is a more reliable way to establish the diagnosis of renal dysfunction. Urine output can be monitored in almost any individual; therefore, it is the most reliable and easiest way to assess renal function in the acute setting.

ETIOLOGY

Although the term used to describe renal dysfunction has changed, the way we evaluate etiology of renal impairment generally remains the same. The traditional way of classifying renal dysfunction as due to prerenal, intrinsic renal or post renal causes remains valid.

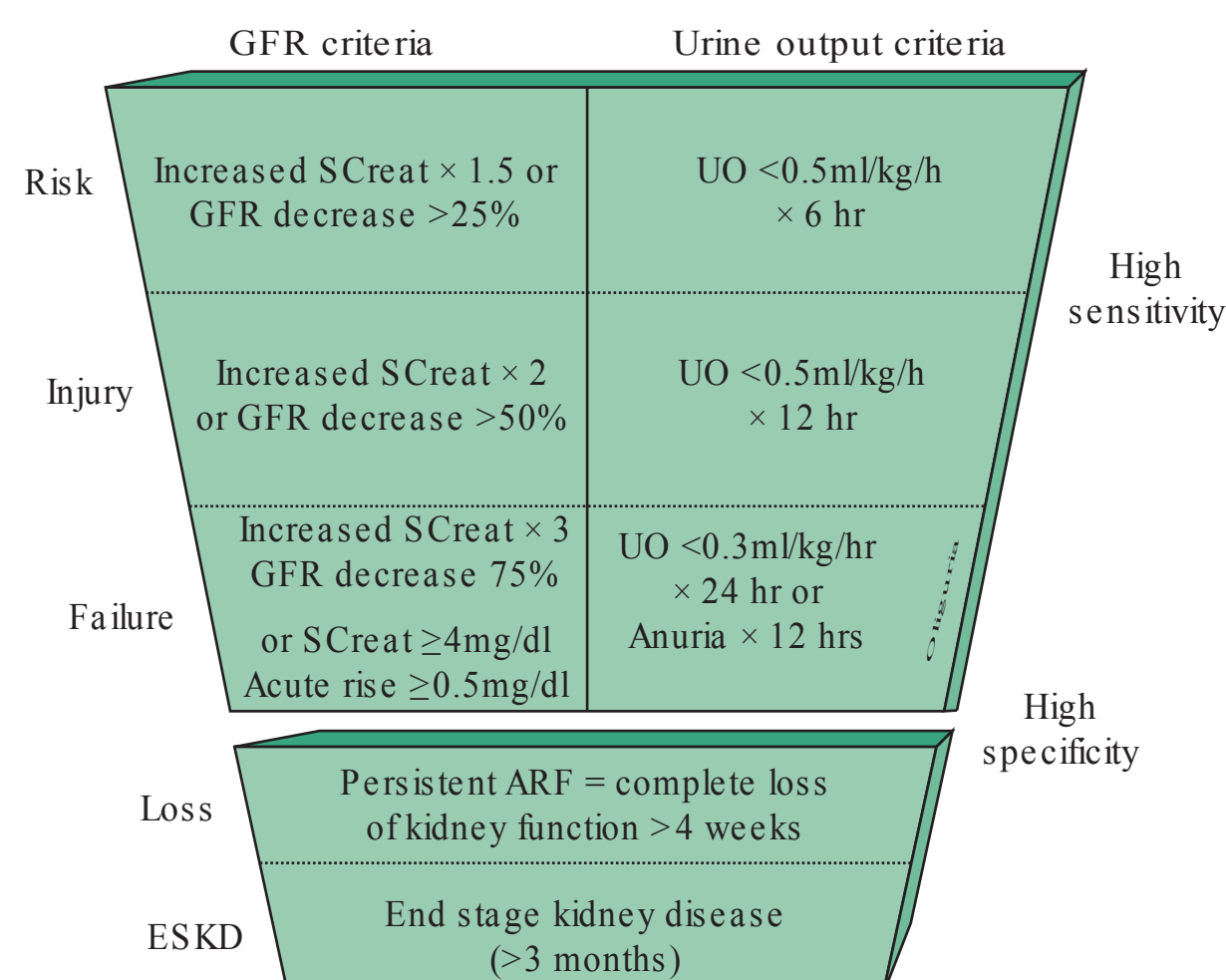


FIGURE 29-1 The RIFLE criteria. (Reproduced with permission from Acute Dialysis Quality Initiative [ADQI], <http://www.adqi.net>.)

Prerenal

Prerenal AKI is traditionally thought of as a result of decreased circulating blood volume, or hypovolemia, and can be from a variety of causes, including dehydration, hemorrhage, systolic heart failure, or liver failure. It is overall a result of decreased blood flow to the kidneys. These causes can often be quickly and easily addressed, resulting in the improvement or complete resolution of the kidney injury.

Diagnosis and treatment of prerenal AKI due to dehydration/hypovolemia is easily assessed and treated with restoration of intravascular volume with crystalloids. Vomiting and diarrhea are commonly encountered causes of hypovolemia in the emergency setting. Hemorrhage-associated prerenal AKI should be treated with the appropriate volume and ratio of blood products, both to restore intravascular volume and to assist in achieving hemostasis.

In the setting of heart or liver failure, the overall total body fluid balance may be grossly overloaded, but the forward flow, or cardiac output, may be decreased as a result of the underlying pathogenetic process of the cardiac or liver disease. Management strategies and goals are discussed here.

CARDIORENAL SYNDROME

Cardiorenal syndrome (CRS) is seen in the setting of systolic cardiac failure and is defined as a reduced GFR through mechanisms that will be discussed later. It has been classified into several types based on the chronicity of symptoms or whether heart failure is due to other conditions, including diabetes or sepsis⁸ (Table 29-1). Decreased GFR in the setting of heart failure is associated with a worsened prognosis and an increase in mortality, thus is an important entity to recognize and treat.

Although precise mechanisms are not well understood, many believe that renal injury in the setting of decompensated heart failure is multifactorial. In a subanalysis of the ESCAPE trial, Nohria evaluated the use of cardiac index as a



TABLE 29-1: Classification of Cardiorenal Syndrome

Type 1	Acute in nature. Acute heart failure resulting in acute kidney injury
Type 2	Progressive in nature. Chronic heart failure resulting in chronic kidney disease
Type 3	Acute worsening of renal function due to renal ischemia or glomerulonephritis that causes acute cardiac decompensation and possibly heart failure
Type 4	Chronic kidney disease that leads to cardiac disease (heart failure, arrhythmia, or CAD)
Type 5	A secondary type of CRS in which a systemic condition results in cardiac and renal dysfunction.

Data from Ronco C, Haapio M, House A, et al. Cardiorenal Syndrome, *J Am Coll Cardiol*. 2008 Nov 4;52(19):1527–1539.

marker of worsening renal function and found no correlation between a low cardiac index and renal function. It is believed that GFR may actually be a better indicator of renal perfusion and may be more useful in the diagnosis of CRS.⁹

In the setting of heart failure, decreased GFR occurs by several proposed mechanisms, including decreased renal perfusion, increased renal venous pressure, and right ventricular failure. As previously stated, patients in decompensated heart failure are total body fluid overloaded, with increased venous pressures as a result. Decreased right heart function results in decreased left ventricular preload and, ultimately, decreased cardiac output. Increased renal venous pressure occurs in the setting of elevated central venous pressures (CVP) and, although the pathogenetic mechanisms of decreased GFR due to renal venous pressure are not well elucidated, many studies have demonstrated inverse relationships between CVP and GFR.^{10–12}

Management of patients presenting with CRS should be aimed at improving cardiac function, which will, in turn, increase the likelihood of improving the GFR. Diuretics are therefore a mainstay of treatment and should be given judiciously in the setting of volume overload as assessed clinically by jugular venous distention (JVD) and peripheral edema even in the face of elevated blood urea nitrogen (BUN) and creatinine (Cr). In 2013, the American College of Cardiology stated within their heart failure guidelines diuresis in patients with evidence of CRS should continue to eliminate clinical evidence of fluid retention even in the setting of a mild to moderate decrease in blood pressure as long as the decrease remains asymptomatic.¹³ Several studies have demonstrated improved outcomes—specifically, improved mortality benefit—with aggressive fluid removal in patients with CRS even when fluid removal is associated with worsening of renal function.^{14–15}

HEPATORENAL SYNDROME

Hepatorenal syndrome (HRS) is a widely appreciated syndrome that is associated with a very poor prognosis. It is usually seen in patients who have portal hypertension secondary


TABLE 29-2: Clinical Features of Hepatorenal Syndrome

- Oliguria
- Normal urine sediment
- Minimal proteinuria
- Low urine sodium (< 10 mEq/L)
- Rising serum creatinine

to fulminant alcoholic hepatitis, cirrhosis, or long-standing liver disease, but can be seen in a patient with hepatic failure of any etiology. HRS is a diagnosis of exclusion; patients must meet specific clinical criteria to carry the diagnosis. Other causes of AKI should be fully evaluated and ruled out as causes of the patient's renal dysfunction prior to assigning the diagnosis of HRS. These criteria include liver disease with portal hypertension, oliguria, an elevated or rising serum Cr, scant protein in the urine (< 500 mg/daily), a urine sodium concentration of < 10 mEq/L, and are usually noted to have normal urine sediment (Table 29-2). The syndrome is usually precipitated by an acute condition, including gastrointestinal bleeding or a bacterial infection of any etiology. Spontaneous bacterial peritonitis should be strongly considered as a precipitating cause of HRS in these patients.

Two types of HRS have been described, type 1 and type 2. Type 1 HRS tends to be more severe and sudden in onset. Type 2 has a rise in creatinine that is less severe, more insidious in onset, but is classically associated with ascites refractory to diuretic treatment. It is important to keep in mind that patients with liver disease may present with seemingly normal Cr values, but can have a marked decrease in their GFR. This discrepancy is explained by the overall poor condition of the patient, including poor protein intake and a reduced muscle mass.¹⁶⁻¹⁷

Treatment of HRS is based on the etiology. Acute decompensated hepatic failure should be treated with appropriate therapy, including abstaining from alcohol in the setting of acute alcoholic hepatitis and treatment with antiviral medications in the setting of acute fulminant viral hepatitis. The primary goals of treatment include increasing the mean arterial pressure (MAP) with the use of vasopressors, including norepinephrine and vasopressin if the patient is admitted to the ICU or midodrine and octreotide if the patient does not otherwise require an ICU setting, and establishing a euvolemic, intravascular state with albumin administration. In some cases, the use of continuous renal replacement therapy (CRRT) is necessary to support renal function while the etiology of liver failure is treated. In patients who are refractory to medical therapy, a transjugular intrahepatic portosystemic shunting (TIPS) procedure may be considered. TIPS procedures should be viewed as a last resort in patients with refractory HRS as the procedure is associated with its own complications, requires the administration of contrast dye, and not infrequently, patients with HRS are too ill to undergo the procedure. Liver transplantation should be considered. The only way to potentially correct the renal injury is

to correct the hepatic function by treatment of the underlying condition or liver transplantation.¹⁸⁻¹⁹

Intrinsic Renal

Intrinsic renal etiologies are more complex to treat and require a more complex evaluation to determine the cause. Intrinsic disease incorporates interstitial, glomerular, and tubular disease. The most common cause of AKI in critically ill and hospitalized patients is acute tubular necrosis (ATN). Glomerular causes can be distinguished using urinalysis to evaluate for proteinuria; although this does not provide a definitive diagnosis, the presence of proteinuria can be helpful.

GLOMERULAR DISEASE

Determining if AKI is due to glomerular disease, such as acute glomerulonephritis, can be differentiated using urinalysis to determine if the process is primarily a nephritic or nephrotic pattern. There are many etiologies for either pattern and, often, there is considerable overlap between the two. Nephrotic patterns are seen with significant proteinuria (usually > 3.5 g/24 h), few casts, and urinary sediment, while unassociated with histologic changes of the kidney. Nephritic patterns are associated with various types of casts (red blood cell, white blood cell, and granular/cellular), and are associated with urine sediment. Proteinuria is highly variable in nephritic patterns (Table 29-3). The evaluation for cause of glomerular disease often involves extensive laboratory investigation, and often requires renal biopsy, all of which are more appropriately done in the inpatient setting rather than the ED.

PHARMACOLOGIC

The use of nonsteroidal anti-inflammatory drugs (NSAIDs) or angiotensin-converting enzyme (ACE) inhibitors are two commonly prescribed medications and can also contribute to pseudo-prerenal causes of AKI through altering the normal autoregulatory mechanisms of the kidney and decreasing arteriolar blood flow, thereby negatively affecting GFR. Sodium excretion is also decreased when using NSAIDs. Patients most at risk for the renal side effects of these medications include patients with preexisting renal impairment and patients with volume depletion.

Treatment for AKI due to medications is usually as simple as discontinuing the offending agent. Renal function will


TABLE 29-3: Nephrotic and Nephritic Patterns

Nephrotic Patterns	Nephritic Patterns
<ul style="list-style-type: none"> • Proteinuria (> 3.5 g/day) • Few casts • Little urine sediment • Edema • Hyperlipidemia 	<ul style="list-style-type: none"> • Variable degrees of proteinuria • Red or white cell casts are common • Often associated with evidence of inflammation on histologic evaluation

normally improve over the following days to weeks without any additional intervention required. Hospitalization for AKI related to NSAIDs or ACE inhibitors is rarely indicated or necessary.

CONTRAST-INDUCED NEPHROPATHY

Contrast-induced nephropathy (CIN) is a widely appreciated decrease in the renal function of a patient who has received intravenous (IV) contrast in the preceding 48 to 72 hours, defined as an increase in serum Cr by 25% from baseline or a total increase of 0.5 mg/dL from an absolute Cr value. Most patients presenting to the ED with AKI will therefore not be candidates to receive IV contrast for radiologic imaging, but the emergency medicine provider should be conscious of the risks associated with the administration of IV contrast. Patient factors that increase their risk for developing CIN include advanced age, history of chronic kidney disease, presence of hypertension and diabetes, history of a renal transplant, and those with hypotension or evidence of systemic hypoperfusion. Repeated or high-dose contrast administration also increases the risk of developing CIN. Although CIN is usually a temporary insult that resolves within 7 to 14 days, it can, in certain patients, result in the need for hemodialysis (HD), with an increased risk in patients with diabetes and preexisting renal dysfunction. In patients without risk factors, the risk of requiring HD is less than 1%. However, in those with diabetes and/or chronic kidney disease, the risk increases to as high as 12%.²⁰

SEPSIS

Sepsis is a common cause of AKI in critically ill patients.²¹ There are several mechanisms by which sepsis is believed to contribute to renal injury; currently, however, there is no one pathway that is fully understood or can completely explain the AKI associated with sepsis. Importantly, AKI in the setting of sepsis is an independent predictor of mortality, therefore needs to be aggressively treated.

Patients presenting with symptoms of sepsis are often found to be hypotensive and demonstrate signs of hypoperfusion. Therefore, it is not difficult to believe that hypoperfusion leads to ischemic ATN and resultant AKI. However, there are several additional theories that offer pathogenetic mechanisms by which sepsis causes AKI. Endotoxemia is believed to be associated with inflammatory mediator release, endothelial injury, and renal vasoconstriction (micro- and macrovasculature), both of which are believed to worsen renal function.

Postrenal

Postrenal causes of AKI are almost always obstructive in nature and can often be reversed quickly, as in prerenal causes. The majority of postrenal AKI in the community is due to obstruction. The most common cause of postobstructive nephropathy is prostatic disease (hypertrophy or malignancy). Bilateral obstruction needs to occur to create a change in the overall GFR; thus, obstruction of a single kidney usually does not result in renal impairment. When

considering obstruction as an etiology of postrenal AKI, one should consider both causes occurring within, and external to, the organ itself. Intrarenal causes include cast formation seen in multiple myeloma, which results in tubular obstruction; crystal formation, as seen in ethylene glycol ingestion; and tumor lysis syndrome, to name a few. Most patients from the community who have external causes of obstruction include prostate disease or pelvic/retroperitoneal disorders, which can result in compression or other mass effects on the genitourinary system.

GENERAL MANAGEMENT

The goals of treatment in the ED should be based on reversing the suspected or identified cause of the patient's AKI, correcting metabolic disturbances present due to AKI, supporting the patient to prevent additional insult to the kidneys, and determining the need for emergent dialysis, if one exists.

Placement of a Foley catheter is almost always indicated in any etiology of AKI, and can be therapeutic in obstructive etiologies. Catheterization will allow for close urinary output monitoring, response to treatment, and will allow the physician to further define the degree and severity of AKI that a patient has.

A chest radiograph and EKG should be obtained to assess for pulmonary edema and evidence of electrical disturbance most commonly due to hyperkalemia. Laboratory studies for the initial evaluation of AKI should include a serum BUN and Cr, myoglobin or creatine kinase to assess for rhabdomyolysis, fractional excretion of sodium (FeNa) to help determine ATN or hypovolemia, phosphorus, ionized calcium, and serum bicarbonate levels. A urinalysis (if urine is produced) should be obtained to assess for protein, cellular casts, and blood to help evaluate for intrinsic renal disease.

Establishing the patient's volume status in the setting of AKI should be a primary goal of the treating physician. The patient's history and the physician's physical exam findings can usually be reliable indications of volume status. Most commonly, prerenal AKI is due to hypovolemia (as in intractable nausea and vomiting or diarrhea and sepsis) and IV fluids should be given. Rapid intervention and treatment of hypovolemia can limit ongoing injury to the kidneys and may help to prevent worsening ATN. The initial fluid of choice for resuscitation should be crystalloid. Colloid can be used, but studies have not shown a difference in outcomes or any additional benefit with using colloids. Crystalloid solutions that contain potassium should be avoided. The total volume of fluids that should be given is patient dependent and should be given with consideration of a patient's comorbid conditions. Endpoints including urine output and MAP (or cardiac output/index if invasive monitoring is available) should be utilized as an indication of sufficient resuscitation. The use of vasopressors in the treatment of septic shock may be necessary despite continuing and seemingly adequate and ongoing fluid resuscitation.

Patients who are clearly volume overloaded or in heart failure should be treated with diuretics rather than IV fluids,

which may actually further worsen their AKI. If CRS or HRS are suspected etiologies, the balance between total body volume overload and intravascular depletion resulting in decreased GFR and AKI is a difficult one to strike. Fluids, if given, should be done judiciously and with frequent assessment for response. Consultation of inpatient colleagues (medicine or critical care) should be strongly considered prior to intervention with patients suspected of having CRS or HRS.

The presence of a metabolic acidosis is not uncommon in AKI due to the body's inability to properly and adequately excrete acids, which are then buffered by the body's sodium bicarbonate. The result is a low serum bicarbonate level and an anion gap metabolic acidosis. Acidemia can have several effects on the body, including alteration of mental status, hyperventilation as a means of attempting to compensate, decreased myocardial contractility, and decreased sensitivity to vasopressors/catecholamines. The majority of the time, the metabolic acidosis is mild and will improve with the treatment of the underlying cause of AKI. However, the decision to actively treat a metabolic acidosis due to AKI/ARF should be based on the severity of the acidosis. In general, a pH of < 7.15 is an appropriate threshold at which to administer sodium bicarbonate. Small aliquots should be administered with the goal pH of no greater than 7.25 or the serum bicarbonate no more than 15 mEq/L. It is imperative to monitor the serum potassium while administering sodium bicarbonate, as it may decline with the increase in the pH.

Imaging

Imaging is often helpful only when considering obstructive etiologies of AKI. A plain abdominal radiograph can be obtained, but few renal stones are well visualized on radiograph. If nephrolithiasis is suspected as the cause of obstruction/AKI, noncontrast computed tomography (CT) is the modality of choice. Although not needed to assess for stones, if contrast is desired for CT imaging of a patient presenting with AKI, this should be carefully considered. If deemed absolutely necessary, the patient should be adequately hydrated with simple crystalloid to prevent additional injury to the kidneys. CT scan also allows for assessment of the retroperitoneal space as an etiology for AKI.

Renal ultrasound (US) can be obtained or performed at the bedside to assess for evidence of hydronephrosis and outlet obstruction. It is a noninvasive study that does not expose the patient to radiation and that can be done quickly. Renal US has several limitations, including operator experience, degraded or difficult imaging due to the presence of bowel gas, and overall, when compared to CT, is not as sensitive or specific. If radiation exposure is of concern, as in pregnant women and children, US may be a good initial test of choice to assess for urinary tract obstruction and evidence of hydronephrosis.

Medication Dosing

Proper medication dosing in a patient with AKI is imperative in the ED to not worsen a patient's renal injury. Consultation

with your pharmacist regarding appropriate antibiotic dosing for patients with presumed sepsis, or avoidance (if possible) of nephrotoxic agents altogether, should be strongly considered.

Renal Replacement Therapy

Initiation of renal replacement therapy (RRT) is relatively uncommon in the ED setting; however, there are several indications in which emergent RRT is necessary in patients presenting with AKI. These indications include severe electrolyte derangements, specifically hyperkalemia, that are resulting in hemodynamic instability or arrhythmia and are refractory to pharmacologic treatment, life-threatening fluid overload leading to respiratory or cardiac failure, uremia (presenting as pericarditis or altered mental status), severe metabolic acidosis ($\text{pH} < 7.1$), symptomatic ethylene glycol ingestion, and severe rhabdomyolysis. AKI requiring RRT has been demonstrated to be an independent risk factor for the development of chronic renal disease, specifically stage 4 or 5. It has also been shown to increase a patient's risk of death by twofold.²²

See Chapter 30, Renal Replacement Therapy, for additional information on indications, initiation of, and management of RRT.

CONCLUSION

AKI is a complex and often multifactorial problem. The differential diagnosis can be quite lengthy, however; often, in the emergency setting, there are several main culprits. The basis of treatment depends primarily on fluid status, which can be quickly assessed with reasonable certainty by a savvy physician. It is important to assess and treat not only the hemodynamics of the patient, but also to rapidly determine if an indication for emergent hemodialysis exists. RRT carries a significant increase in mortality, but more so is a risk factor for the development of significant, lifelong renal disease.

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Renal Replacement Therapy

Tara A. Paterson • Deborah M. Stein

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INTRODUCTION

In keeping with the role of providing organ support, such as management of a ventilator for pulmonary support or administration of pressors and inotropes for cardiovascular support, it is often the intensivist's role to provide support for failing kidneys. This chapter will focus on when and how to provide that support.

Normally functioning kidneys are important in several homeostatic mechanisms:

1. The production of hormones, such as erythropoietin and renin
2. Partial conjugation required to activate vitamin D that is necessary to absorb enteral calcium

3. The regulation of acid–base status
4. The filtration of blood and regulation of solute concentrations, such as sodium and potassium
5. The elimination of fluid and waste products such as urea

The focus of this chapter will be a description of how to appropriately assist or replace these last three functions of the kidneys, namely, maintenance of normal acid–base status, solute clearance, and volume and waste product removal.

RENAL FAILURE

Depending on the population studied, the incidence of acute renal failure (ARF) in intensive care unit (ICU) patients has

been reported to be as high as 25%.^{1,2} There is disparity, however, in how ARF is defined in clinical practice as well as in the literature. This has led to initiation of renal support at different levels of renal function, which makes it difficult to compare studies, construct studies, or extrapolate findings in daily practice. Furthermore, what was previously known as ARF is now described along a spectrum of renal dysfunction, more appropriately termed acute kidney injury (AKI).

The Acute Dialysis Quality Initiative Group (ADQI), a group formed in 2000 “to provide an objective, dispassionate distillation of the literature description of the current state of practice of dialysis and related therapies,”³ proposed a now commonly used classification scheme for diagnosing ARF.⁴ Commonly referred to as the RIFLE criteria, the acronym itself describes the level of renal dysfunction:

- R—Risk of renal dysfunction
- I—Injury to the kidney
- F—Failure of kidney function
- L—Loss of kidney function
- E—End-stage kidney disease

Each level (R-I-F-L-E) of renal dysfunction can be classified or diagnosed by changes in the glomerular filtration rate (GFR) and/or serum creatinine or reduction in urine output (UO).

The GFR is generally considered a better measure of renal function/failure, although it is typically measured only via surrogates such as creatinine clearance. Interpreting a change in GFR requires knowledge of the baseline creatinine that is not always available. Assuming normal baseline renal function, however, the ADQI group has developed a theoretical baseline serum creatinine value for a given patient normalized to body surface area and based on age, race, and sex.⁵ In the event that a normal baseline creatinine cannot be assumed, UO can also be used to define acute renal dysfunction. The advantage of UO is that it can be used on all patients except for patients anuric prior to their acute illness (i.e., patients with end-stage renal disease already on dialysis) or in whom UO cannot be accurately measured (i.e., patients with bladder injury and persistent urine leak). The ADQI group released a graphical representation of the criteria, as shown in Figure 29-1. The diagram refers to AKI and sensitivity (S_n) of classification criteria. The criteria at the bottom of the diagram have a lower S_n and may have a higher risk of false negatives. However, these criteria have a high specificity (S_p), more likely to have true AKI and a lower risk of false positives.

As more studies use the ADQI Group’s RIFLE criteria, it will likely become easier to compare studies with each other, and to identify studies whose populations are similar to one’s own population, leading to better evidence-based approaches.

WHEN TO INITIATE RENAL SUPPORT

The indications for initiating renal support can be remembered by the mnemonic AEIOU RSI:

- A—Acidosis
- E—Electrolyte abnormality

- I—Intoxication, Ingestion, and Immune modulation (still controversial)
- O—Fluid Overload
- U—Uremia
- R—Rhabdomyolysis
- S—Sepsis (and multiorgan failure, still controversial)
- I—IV contrast (with renal insufficiency (RI) or ARF)⁶⁻⁸

Renal support should be initiated if the patient has any of these indications. In the case of patients who will receive IV contrast, this is particularly true if the patient has baseline RI that is resistant to conservative treatment such as intravenous (IV) hydration.

BACKGROUND FOR RENAL SUPPORT

Renal replacement therapy (RRT) is a therapy designed to clear the blood of solutes and volume that normal functioning kidneys remove. The most commonly measured substances cleared by RRT are potassium and urea. There are two broad categories of RRT: intermittent renal replacement therapy (IRRT) and continuous renal replacement therapy (CRRT). IRRT or intermittent hemodialysis (IHD) is the most commonly used therapy.

IHD in chronic renal failure (CRF) and end-stage renal disease (ESRD) is performed on a regular schedule in an outpatient setting or dialysis center. Patients typically receive IHD for 3 hours, three times per week. By following a specific lifestyle, such as a “renal” diet and limiting fluid intake, these sessions are enough to remove solutes and fluid, and thereby approximate what normal human kidneys accomplish with continuous normal renal blood flow. When such patients are admitted to a hospital (for renal or unrelated issues), they should receive their normal IHD sessions, with adjustments made for their acute illness. Such sessions can be run at the patient’s bedside or, if stable for transport, the patient can be moved to the hospital’s dialysis center.

The advantage of IHD is cost, in terms of both time and resources. IHD requires a specialized nurse, but only for ~9 hours per week. The general disadvantages of IHD are the requirement of large vascular access (usually initially done with a long-term indwelling dual-lumen vascular catheter or a surgically constructed arteriovenous fistula or graft, that is, a “shunt”) and the time commitment required to attend a dialysis center three times per week for ~3 hours each time. Another major disadvantage is the accumulation of substances such as potassium and urea and body fluid both as increased blood volume and peripheral edema over days between IHD sessions, then rapid resolution in a single IHD treatment. These shifts are obviously not as physiologic as the continuous clearance performed by the patient’s own kidneys but generally well tolerated by the vast majority of patients with CRF and ESRD.

Emergency physicians are acutely aware of this issue since patients with dialysis disequilibrium may present to the ED. In addition to lesser symptoms, such as headache, vertigo, and weakness, dialysis disequilibrium can cause seizure, intracerebral hemorrhage, cerebral edema, and even death.⁹

Among outpatients with CRF, however, an alternative to traditional IHD is peritoneal dialysis (PD). There are 2 versions: continuous ambulatory peritoneal dialysis (CAPD), which is done manually, and automated peritoneal dialysis (APD), which is done with a machine called a cycler. Patients who are candidates for PD typically are patients who are unable to maintain adequate vascular access, cannot tolerate the rapid changes of fluid balance associated with IHD, or are immobile or live in remote areas without easy access to a center for IHD. For PD, a catheter is surgically implanted into the patient's peritoneal space. The patient, a health care aide, or an automated machine (at night, while the patient sleeps) adds fluid via the access port. The dialysis fluid remains in the abdomen, equilibrating with the patient's interstitial fluid, called the dwell. The fluid, along with solutes and electrolytes (such as urea and potassium), is then drained and discarded, and new fluid is added. This must be done manually several times per day or automatically with APD several times overnight. The primary advantages of PD are 2-fold. First, it avoids the chemical and fluid shifts associated with an intermittent build-up between traditional HD sessions and then rapid removal over a several-hour IHD session. Second, it is convenient since a reliable patient can administer this therapy oneself at home. The main disadvantages of PD are complications related to the catheter, such as local infection (cellulitis) or peritonitis, which can be extremely morbid, and cardiac and pulmonary dysfunction related to negative effects on diaphragmatic excursion secondary to the excess intra-abdominal fluid.¹⁰

Outpatient modalities, however, are often not appropriate for use in the ICU for a variety of reasons. Since, as previously discussed, up to 25% of ICU patients will develop ARF at some point during their illness, intensivists should be knowledgeable about how to support the kidneys as they would support any other organ.

Whether the AKI is transient and will resolve as the patient clinically improves or will become permanent, a patient in ARF often will require some renal support. If AKI progresses to renal loss or ESRD, patients may eventually require outpatient IHD as described earlier. While in the acute phase of illness, however, it is difficult to determine if a patient's renal function will recover. Furthermore, even for patients who were already on IHD, a critical illness may prevent the safe utilization of IHD.

One reason that IHD in a patient with critical illness may not be preferred has to do with the fact that critically ill patients often become nutritionally deficient. To maintain a patient on every-other-day IHD, it is necessary to restrict fluid and, just as important, protein intake. When on CRRT, patients can receive liberal volume administration and can be fed either enterally or parenterally without concern of urea accumulation. In other words, there is no need to limit feeding for patients on CRRT while there is such a limitation for patients receiving IHD.

High blood flow volumes required for effective IHD can cause hypotension at time of initiation. This hemodynamic instability, however temporary, has been reported to cause loss of consciousness and myocardial infarction (MI), and

has even caused patients with RI to progress to complete renal failure.¹¹ Furthermore, for patients with hemodynamic instability, IHD may be contraindicated. In the past, some of these patients were treated with PD, but clearance of solute may not be sufficient. Patients with abdominal injury or infection are not candidates for PD.¹²

Additionally, patients in the ICU with either a primary intracranial event (i.e., traumatic brain injury [TBI], stroke, nontraumatic intracranial hemorrhage) or at risk for elevation of intracranial pressure (ICP; i.e., cerebral edema, hepatic encephalopathy, hepatic failure), IHD may not be advised. IHD causes abrupt shifts in intravascular volume and may alter ICP and cerebral perfusion pressures due to hypotension.^{13,14}

THE FINAL ARGUMENT

Despite the number of critical care patients who may have contraindications to IHD, many feel that if a patient can tolerate it, IHD should be the preferred modality, mainly due to cost. Despite countless studies that have attempted to demonstrate a reduction in mortality and morbidity with the use of CCRT, conclusive benefit has not been proven.^{15–18} If IHD is to be used due to resource constraints, sustained low efficiency dialysis using a single-pass batch dialysis system (SLED-BD) may be preferable.¹⁹

As previously mentioned, lack of standardization in initiation of RRT, modalities settings used, and clinical indicators used to terminate therapy make reviewing the literature a challenge. However, several key concepts about potential benefits of CRRT can be gleaned from the available literature. Kellum et al. performed a meta-analysis and found that, after pooling studies that enrolled patients with similar APACHE II scores, mortality was lower in patients treated with CRRT.²⁰ Furthermore, when adjusted for study quality and severity of illness, mortality was still noted to be lower in patients treated with CRRT. However, the quality of the studies evaluated did not allow for a conclusion that CRRT demonstrated definitive benefit over IHD. The other main conclusion of this study was that, again, due to the quality and diversity of CRRT management in the studies, it was not possible to determine the optimum timing, modality, and dose of CRRT. Perhaps the most convincing evidence for a suggestion of mortality benefit was an unexpected conclusion from Jacka et al.²¹ In this study, the investigators found that, among patients who survived their critical illness, those who received continuous veno-venous RRT, as opposed to IHD, were more likely to recover their renal function and not require long-term or permanent IHD.²¹ A similar conclusion was also drawn by Waldrop et al.,²² though not proven since their study was underpowered to detect this outcome. This study did draw two important conclusions: (1) Patients who suffer ARF secondary to a critical illness have such a high mortality from their inciting event that the massive mortality risk obscures any small benefit CRRT might incur. (2) Perhaps studies have been evaluating the wrong endpoint and should instead be powered to study recovery of renal function after CRRT versus IHD, rather than mortality benefit.

Finally, one common theme stands out among all the studies; hemodynamics. One absolute indication for CRRT over IHD is hemodynamic instability (i.e., hypotension) precluding the safe initiation of IHD. Such a degree of hypotension is clearly an indicator of sicker patients. Therefore, all of the literature is limited by the fact that it is difficult to randomize patients to IHD or CRRT due to this difference and the fact that these patients are as clinically appropriate, treated with CRRT rather than IHD. One interpretation of this is that CRRT may be demonstrating itself to be a superior modality by achieving survival rates with sicker patients comparable to that achieved by IHD with healthier patients.

THE BASICS OF CRRT

At its core, CRRT is very similar to IHD. In each modality, blood is removed from the patient, filtered or “cleaned,” excess fluid is removed, then the blood is returned to the patient.

In the most basic of CRRT setups, Figure 30-1, blood is removed from the patient at a rate called the blood flow rate, or Q_B . It is passed through a hydrostatic pump that contains a filter with pores. If a convective force is generated, such as with continuous venovenous hemofiltration (CVVH) or if a countercurrent, diffusive force is present, such as in continuous venovenous hemodialysis (CVVHD), any solute dissolved or suspended in the fluid that is smaller than the size of the pores (such as potassium and urea) will pass through. Different filters have different size pores, but generally the pore sizes are 500 to 50,000 daltons, large enough to allow passage of fluid and solutes, but small enough to prevent loss of plasma proteins such as albumin (80,000 d). This allows fluid and small solutes to be removed without also removing plasma proteins or cells. The remainder of the blood is then returned to the patient.

Blood is returned through a central vein; however, the blood draw line can be placed in an artery or a vein. If blood is drawn from an artery, this is called continuous arteriovenous renal replacement therapy (CAVRRT), usually shortened to CAVRT or CAVH where the H stands for hemofiltration (HF). If blood is drawn from a vein, this is called CVVRT (usually shortened to CVVRT or CVVH).

When RRT was first developed, blood was taken from an artery using CAVRT. This allowed for a simpler mechanism because no pump was required. The system used the patient's blood pressure as the driving force to keep blood moving through the system. However, CAVRT had many complications, mostly

due to the arterial cannulation. Tominaga et al. reported arteriovenous fistulas when an adjacent artery and vein such as the femoral vessels were cannulated, pseudoaneurysms, deep vein thromboses (DVTs), ischemia in limbs distal to the arterial cannulation secondary to embolization, and persistent bleeding requiring surgical intervention.²³ They noted that the rates of vascular complications with CAVRT are similar to those of the arterial access for angiograms, suggesting that the complication is related to the arterial cannulation itself, rather than the dwell length of the catheter. In addition to the complications reported by Tominaga et al., Bellomo et al. reported shunt failures requiring revisions, infections, bleeding from the shunt itself, recurrent clotting requiring invasive intervention, and hematomas from failed arterial cannulations.²⁴

Even more important, patients receiving CAVRT have shown a higher mortality compared with those receiving CVVRT.²⁵ It is postulated that this mortality is a result of the lower clearance rates achievable with CAVRT as opposed to CVVRT. In fact, many patients placed on CAVRT required IHD for additional solute clearance.^{19,24–26} Finally, CAVRT requires the patient's heart to do all the work. For patients already hypotensive (one of the major reasons to put a patient on CRRT instead of IHD), this places more demand on a heart already strained, results in lower blood flow, and is a contributing factor to the lesser clearance obtainable with CAVRT.^{19,25}

The main hindrance to CVVRT instead of CAVRT was the pump and circuit technology. Specifically, CVVRT setups require air detectors and bubble traps to prevent air emboli to the lungs, and closer monitoring.²³ Once technology evolved to safely include a pump, CVVRT became the preferred modality. In this setup, blood is drawn from a central vein, “cleaned” by the CRRT setup, then returned to a central vein.

VASCULAR ACCESS

For CVVRT vascular access, a large-bore dual-lumen catheter placed into a central vessel provides a “take blood” line and a “return blood” line in one catheter. If such a catheter is not available, CVVRT can be administered with two independent large-bore, single-lumen, central lines. However, this obviously doubles the risk of cannulation complications.²⁴

CRRT catheters come in a wide variety of lengths and lumen sizes. As a general rule, the larger the lumen size, the better the flow rate. To accomplish higher flow rates that may be required for inflammatory mediator or myoglobin clearance, a larger French catheter is preferable. The benefit of this must be weighed, however, against the increased risk of catheter-related complications such as thrombosis and vessel injury. Catheter lengths should be sized to the vessel cannulated with longer catheters (up to 24 cm) generally used in the femoral position and shorter catheters (16 cm) positioned in the jugular vein. The length and width of the catheter should also be tailored to the size of the patient. According to KDIGO guidelines, the preferred access is the right internal jugular vein for direct access with best flow.⁵ The second preference for access is the right femoral vein, then left internal jugular vein, and last, dominant subclavian vein. Catheters

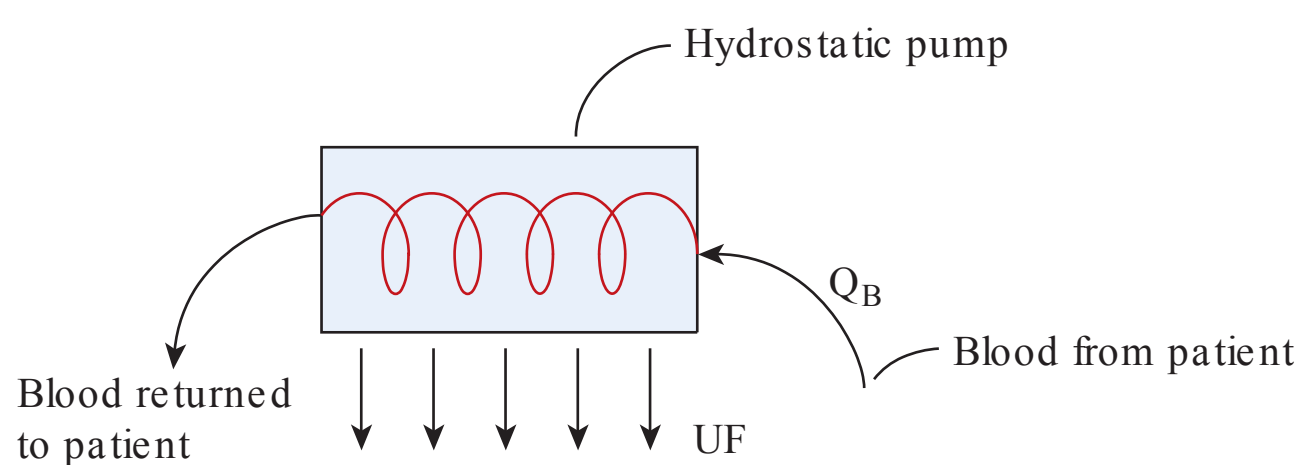


FIGURE 30-1 Slow continuous ultrafiltration (SCUF). UF: ultrafiltrate; Q_B : blood flow.

should be placed using ultrasound (US) guidance. The catheter should be placed as far away as possible from other medication infusion lines. When hooking up the CRRT circuit to the central venous catheter, care should be taken so that the intake line should be upstream from the return line or the circuit will yield a vastly reduced efficiency.

For patients who are dependent on other extracorporeal technology, CRRT can be safely accomplished through the external circuit such as those patients on extracorporeal membrane oxygenation (ECMO) or cardiopulmonary bypass. A hemoconcentrator or full CRRT circuit can be safely introduced and have the “take blood” line come off the other pump.¹⁰ The blood is still returned directly to the patient in these setups.

THE SIMPLEST CIRCUIT—SLOW CONTINUOUS ULTRAFILTRATION (SCUF)

The setup in Figure 30-1 is called slow continuous ultrafiltration (SCUF) and is the most basic of CRRT modalities. The blood is removed from the patient as a set rate (Q_b), and passed through a filter. The ultrafiltrate flow rate (Q_{UF}) or patient fluid removal rate (PFR) is set at a certain mL/h to allow for continuous fluid removal. SCUF is designed exclusively for fluid clearance, as it does not create enough convective force due to low ultrafiltrate (UF) rates to significantly remove small and middle size molecules or solutes via solute drag. It is a very effective way to provide gentle and continuous volume removal such as may be used in patients with congestive heart failure (CHF) or volume overload that may otherwise be treated with a diuretic. The fluid extracted is an ultrafiltrate of plasma. All other CRRT setups build on the foundation of SCUF.

CONTINUOUS VENOVENOUS HEMOFILTRATION (CVVH)

SCUF as shown in Figure 30-1 limits clearance to simple fluid removal. However, consider Figure 30-2. In this setup, blood is removed from the patient at rate Q_b , just as in SCUF. The total flow rate (Q_{UF}) that passes across a filter will determine the degree of clearance of small and middle-sized molecules via *convection*. In SCUF, if high enough flow rates to generate a convective force were achieved (typically $> 1\text{--}2\text{ L/h}$), the blood volume would become unacceptably low and blood would

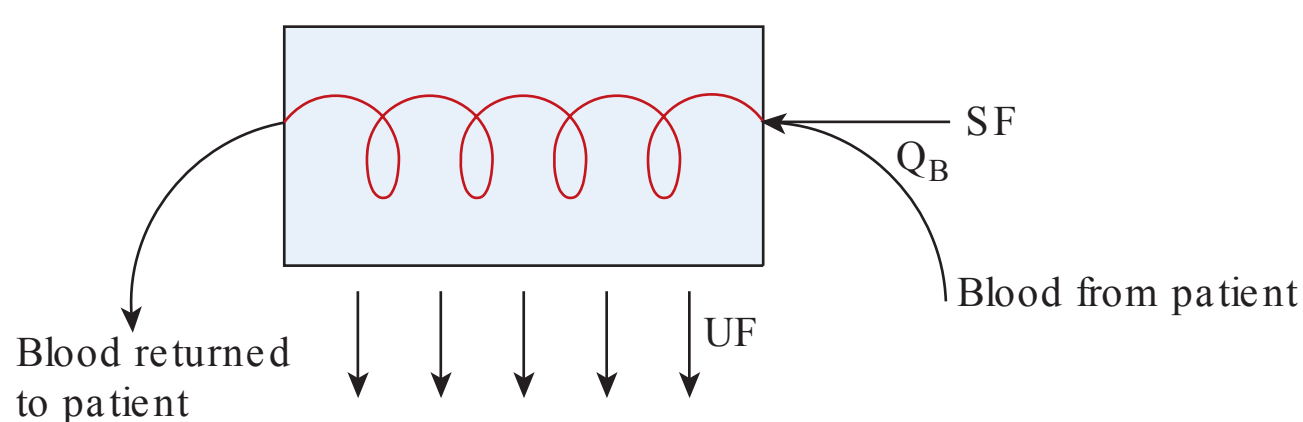


FIGURE 30-2 Continuous venovenous hemofiltration (CVVHF). Substitution fluid (SF) running “prefilter.” UF: ultrafiltrate; Q_b : blood flow.

become unacceptably hemoconcentrated. Therefore, with CVVH, a substitution fluid (SF) or replacement fluid (RF) is added to the blood circuit (typically $2\text{--}6\text{ L/h}$) to make up for the fluid volume that must be removed to create the convective force. Blood with the SF or RF added is then returned to the patient after passing through the filter. Solute removal is accomplished via “solute drag,” in which the solutes are dragged along with the fluid and forced out of the system by convection when high UF flow rates are achieved. Additionally, solute maintenance is accomplished by the choice of SF (Table 30-1).

As an example, consider CRRT in two identical patients. The first will be supported using SCUF, as in Figure 30-1, with the Q_b set to be 100 mL/min . Using SCUF alone, the amount of solute is minimal, as only $\sim 100\text{ mL/h}$ is removed as PFR. For a second patient, supported as in Figure 30-2, the same Q_b of 100 mL/min is set, but also with a Q_{SF} of 2 L/h , enough to generate convective force and solute drag. The Q_{UF} or PFR is set at 100 mL/min to take off the same 100 mL/h of volume, but now with the Q_{SF} applied, the total flow of volume across the filter is 2.1 L/h and clearance of substances is achieved in addition.

A MORE EFFICIENT CVVH SETUP

In Figure 30-2, SF was added to the blood before the combined fluid went through the filter (called “prefilter”). The problem with this method is that the SF dilutes out the blood, then filters the combined fluid (blood + SF). Consider the setup shown in Figure 30-3 instead.

In this case, Q_b is still 100 mL/min . But now, as opposed to the earlier setup, blood is filtered at full concentration. Setting a high Q_{SF} with no PFR clears substances while maintaining an even fluid balance. The advantage of this setup is more efficient filtration (i.e., higher solute and molecule clearance). The disadvantage of this setup is that, as more concentrated solute is pushed through the filter, the filter clogs faster. While it seems a straightforward solution to “simply change the filter,” the technical realities entail halting the system (during which time the patient is receiving no therapy), removing the old filter, and recycling and restarting the system. Error-causing complications—including infection, air emboli, and so on—can be introduced in any one of these steps. An increased number of system halts increases the

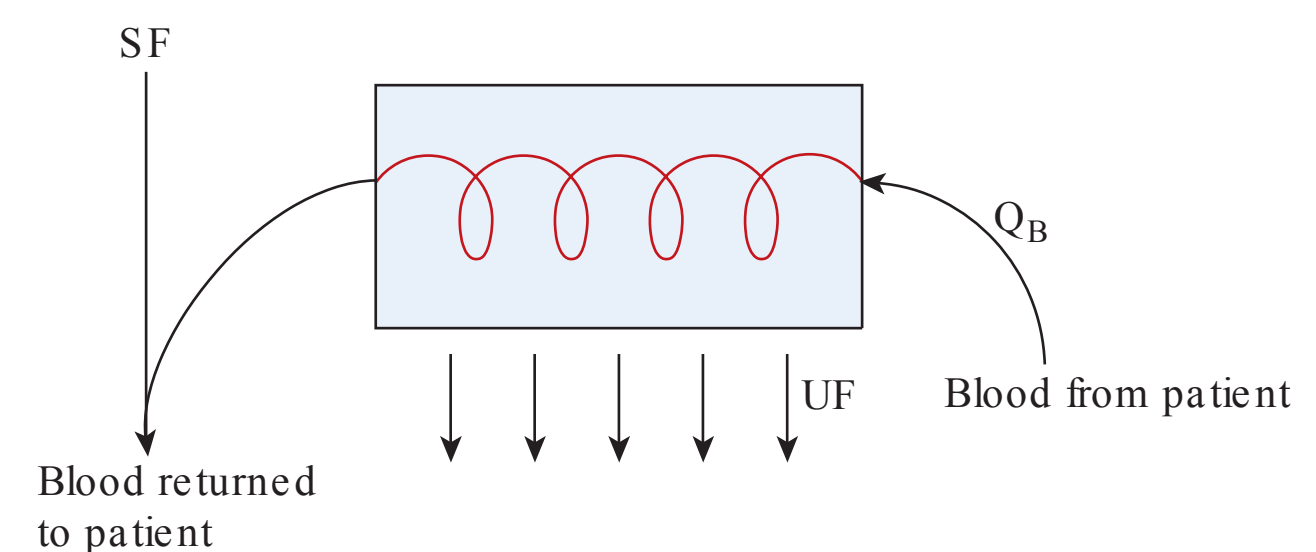


FIGURE 30-3 Continuous venovenous hemofiltration (CVVHF). Substitution fluid (SF) running “postfilter.” UF: ultrafiltrate; Q_b : blood flow.



TABLE 30-1: Commonly Available Solutions Compared to Human Plasma									
	Human Plasma	0.9% NaCl	PlasmaLyte A	Sterile Water with 150 mEq HCO ₃ (3 ampules)	0.45% NaCl with 75 mEq NaHCO ₃ (1.5 ampules)	PrismaSATE® BK0/3.5	PrismaSATE® BGK4/2.5	PrismaSATE® BGK2/0	PrismaSAT B22K4/0
mEq/L)	135–145	154	140	150	152	140	140	140	140
nEq/L)	95–105	154	98	0	77	109.5	113	108	120.5
E/L)	3.5–5	0	5	0	0	0	4	2	4
mEq/L)	1.5–2	0	3	0	0	1	1.5	1	1.5
e (mEq/L)	0.5–2	0	0	0	0	3	3	3	3
s [−] (mEq/L)	22–26	0	0	150	75	32	32	32	22
se (mEq/L)	70–110	0	0	0	0	0	110	110	110
e (mEq/L)	0	0	27	0	0	0	0	0	0
mEq/L)	8.5–10.5	0	0	0	0	3.5	2.5	0	0
larity (mOsm/L)	275–295	308	294	300	300	287	300	292	296



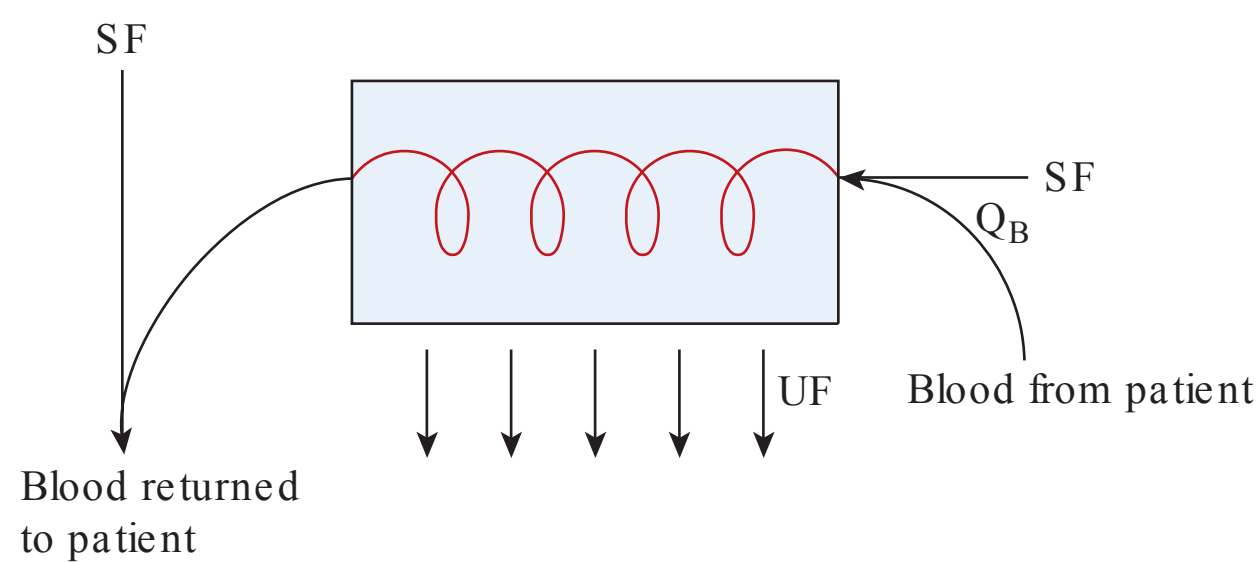


FIGURE 30-4 Continuous venovenous hemofiltration (CVVHF). Substitution fluid (SF) running “prefilter” and “postfilter.” UF: ultrafiltrate; Q_B : blood flow.

number of times that a complication may develop, thereby increases the complication risk as the access ports and other parts of the system are manipulated. It also decreases the efficiency of filtering the blood.

THE BEST OF BOTH WORLDS: PREFILTER AND POSTFILTER

The setup shown in Figure 30-4 is simply a combination of the pre- and postfilter SF (Figures 30-2 and 30-3). In this case, some SF is run prefilter and some is run postfilter. By running some SF prefilter, the solute is diluted, reducing the efficiency of solute clearance but prolonging the life of the filter. As discussed earlier, this reduces the number of times that the filter must be changed, therefore increases the time that efficient therapy is applied and reduces the number of times that complications could occur. Conversely, running some SF postfilter allows for less efficient removal of solutes while maintaining improved filter life.

This combination of running the SF both prefilter and postfilter may provide the best compromise of solute clearance and filter uptime. However, this has not been well studied and there are no studies demonstrating the optimal combination of fluids (e.g., 30% prefilter and 70% postfilter). In addition, this combined approach adds another layer of complexity to an already complex setup.

CONTINUOUS VENOVENOUS HEMODIALYSIS (CVVHD)

Another way to configure CRRT is to use the filter as a diffusive “membrane” rather than a pure filter (see Figure 30-5) called continuous venovenous hemodialysis (CVVHD).

In this case, blood is still withdrawn from the patient at a rate (Q_B). Rather than pure filtration of the blood through the membrane, a countercurrent of dialysate is applied at a given flow rate, the Q_D . The fluid that is applied does not enter the patient’s blood stream, but rather runs countercurrent, allowing for a *diffusive* force to be applied in which solutes will move from fluid with a high concentration to fluid with a low concentration. Diffusible substances such as potassium and urea flow across the membrane down their concentration gradients into the dialysate, which is then discarded as effluent.

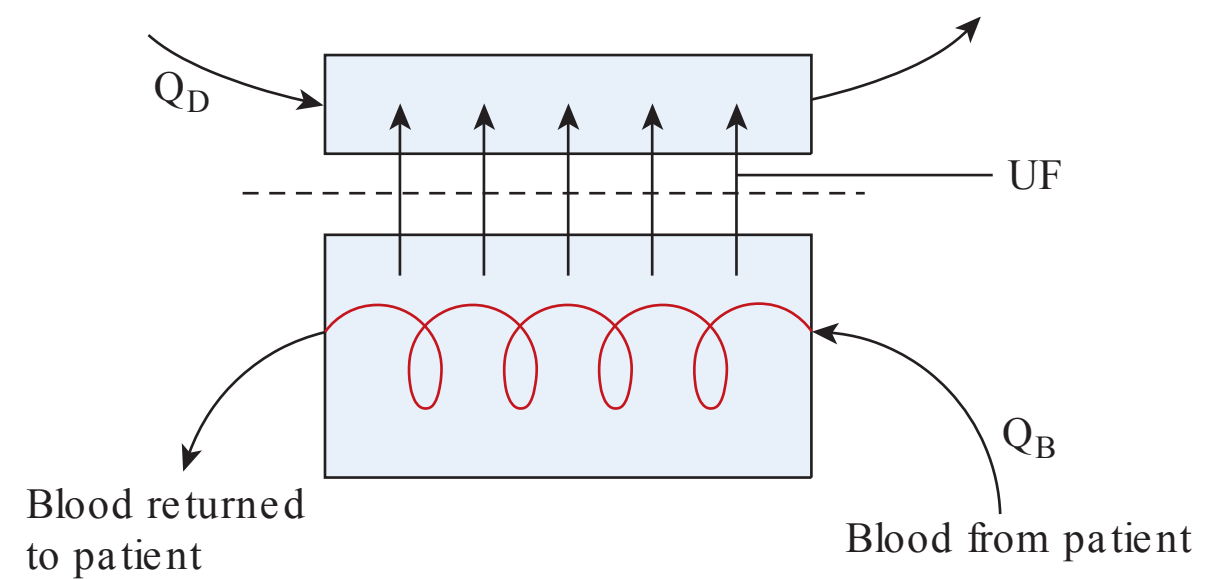


FIGURE 30-5 Continuous venovenous hemodialysis (CVVHD). Q_D : dialysate fluid flow; UF: ultrafiltrate; Q_B : blood flow.

This dialysate runs on the other side of the membrane and is typically the same type of fluid that is applied in the CVVH setup described earlier (Figure 30-2). PFR can still be applied to remove volume as in SCUF or CVVH. Remember, though, since there is no significant flow across the filter with CVVHD, only solute removal is accomplished without any removal of small or middle-sized molecules, such as myoglobin or inflammatory mediators. Therefore, for most toxin, drug, or inflammatory mediator clearance, hemofiltration either as CVVH or CVVHDF (described in the next section) must be applied.

CONTINUOUS VENOVENOUS HEMODIAFILTRATION (CVVHDF)

For maximum clearance, CVVH and CVVHD can be run simultaneously. In certain patients, both convective and diffusive forces to clear both solute and other molecules may be desirable. In this case, one can easily combine CVVH and CVVHD to CVVHDF, in which both Q_{SF} and Q_D are used to combine to 2 modalities. The SF is added directly to the patient’s blood circuit and the volume applied as SF is removed through the filter. The dialysate is applied on the other side of the membrane exactly as in CVVHD and is discarded in the effluent. PFR can also be applied for additional volume removal. Such a setup, complete with prefilter and postfilter SF, anticoagulation with heparin, and prefilter and postfilter blood sampling for adequacy of anticoagulation (discussed later), is pictured in Figure 30-6. Note that

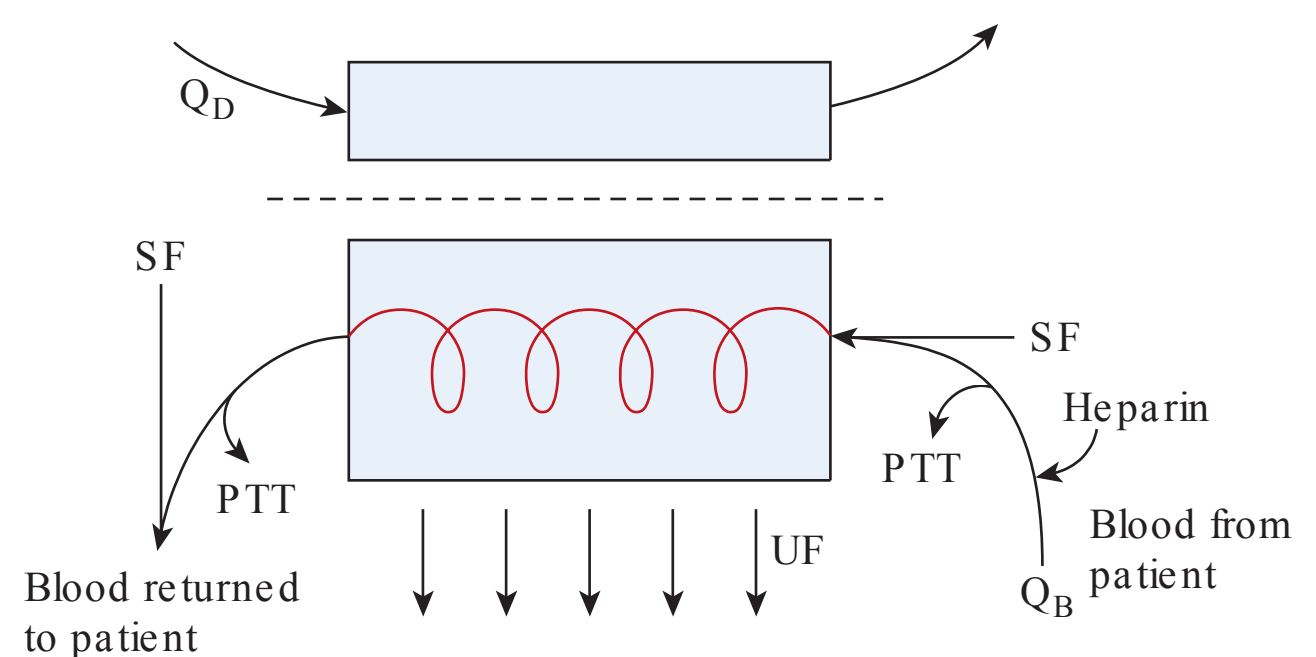


FIGURE 30-6 Continuous venovenous hemodiafiltration (CVVHDF). Q_D : dialysate fluid flow; PTT: partial thromboplastin time; SF: substitution fluid; UF: ultrafiltrate; Q_B : blood flow.

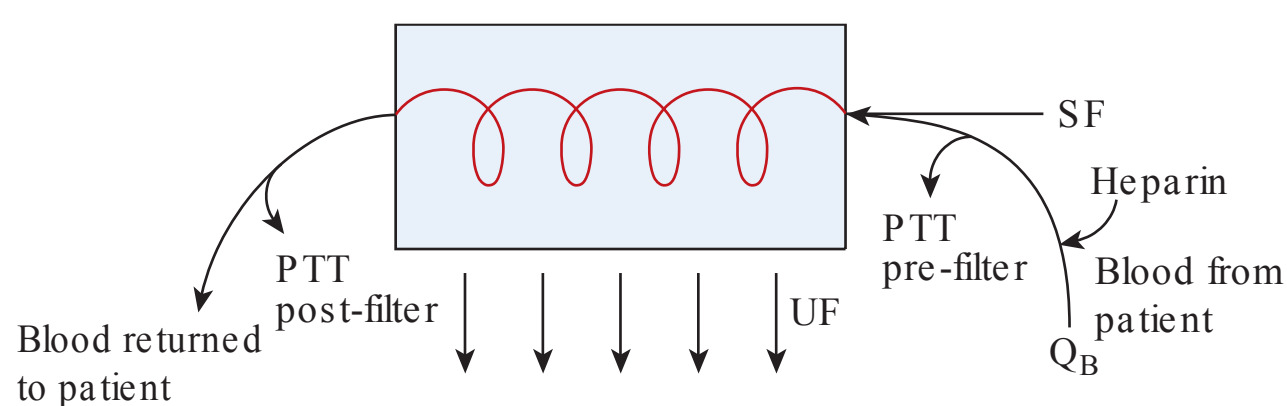


FIGURE 30-7 CVVHF—showing anticoagulation with heparin and location of blood draws for partial thromboplastin time (PTT). SF: substitution fluid; UF: ultrafiltrate; Q_B : blood flow.

covering everything below the dotted line leaves a CVVH circuit as pictured in Figure 30-7. Eliminating the prefilter and postfilter SFs and additional UF leaves the CVVHD circuit pictured in Figure 30-5.

Table 30-2 shows the relative clearances of CVVH versus CVVHD versus CVVHDF. As you can see, CVVHDF results in higher clearance rates, but not exponentially so.

SUBSTITUTION AND DIALYSATE FLUIDS

The selection of a dialysate or SF starts with some basic principles, then moves into the “art” of medicine. It is strongly influenced by the fluids available at a particular institution, the preexisting electrolyte disturbances, and metabolic imbalances of the patient.

Theoretically, as Q_B and SF infusion rates are raised higher and higher, in either CVVH or CVVHDF, the plasma concentrations of solutes will start to approximate those fluids. Therefore, the patient’s current condition should be taken into account when choosing an SF or dialysate. For instance, if a patient is hyperkalemic, it would be prudent to start with a fluid that has no potassium in it. The 0 K^+ fluid will quickly drop the potassium levels and adjustments must be made once the patient’s potassium level normalizes in order to prevent an equally dangerous hypokalemic state. Furthermore, it is known from other sources that most patients do not benefit from exogenous bicarbonate administration in the absence of cardiac effects. However, a patient with cardiac instability from a low pH secondary to a toxic ingestion might benefit from an SF with significant amounts of bicarbonate. Some commonly available SFs are listed in Table 30-1.



TABLE 30-2: Clearance Properties of Different Modalities of CRRT

Modality	Urea Clearance (g/day)	Middle Molecule Clearance
SCUF	1–4	+
CVVHF	22–24	++
CVVHD	24–30	–
CVVHDF	36–38	+++

Three other issues are worth mentioning here:

1. A hospital pharmacist should be able to make an SF or dialysate with almost any concentration of solutes such as sodium, potassium, bicarbonate, and so on. However, it is rather labor intensive to do this for a fluid used at a rate of 2 to 6 L/h. It also introduces another possibility for error since it is nonstandard and must be mixed ad hoc. It is also significantly more expensive than using fluids that are “off-the-shelf.” Custom fluids are generally used only for the rarest of circumstances in which an extra degree of control is required. For instance, it might be useful in pediatrics, in which the smaller body weights limit the amount of fluid one can administer, regardless of the content of that fluid.
2. Consider fluids that make it easier to run the machine. For instance, the PrismaSATE® solutions are often available in 5 L bags, while normal saline is available in only 1 L bags. Therefore, if the patient’s condition will allow PrismaSATE® it is an easier fluid for the nurse to administer, as it only requires a bag change every 5 L, rather than every 1 L. This also reduces the number of manipulations to the system’s lines and reduces the chances for errors to occur.
3. Finally, fluids can be combined. Thus, for someone who is dangerously hyperkalemic, it might be prudent to start with PrismaSATE®0K in order to lower the potassium into a safer range as quickly as possible. As the potassium approaches a normal level, but is still elevated, a bag of PrismaSATE®0K and a bag of PrismaSATE®4K can be connected together with a “Y” connector, effectively giving a new fluid, PrismaSATE®2K. You can also run a 0K solution prefilter and a 4K post-filter. This will still lower the patient’s potassium but minimize the risk of dangerous hypokalemia. When the patient’s potassium normalizes, a switch to a 4K alone will maintain the potassium in the normal range.

FILTER

Although there are different filter configurations for CRRT, because of cost considerations, generally, an institution will have only one or two filters available. In the case that a different filter is desired, or even being considered, it is important to know the differences between the filters. For example, in rhabdomyolysis, you may choose a filter with a bigger pore size to filter larger-sized molecules. Another example is a charcoal filter, which might be used in the setting of toxic ingestion or overdose.

The membranes that compose filters used in CRRT are high-flux synthetic membranes, made of polysulfone, polyamide, polyacrylonitrile (PAN), or polymethyl methacrylate. These membranes can be symmetric or asymmetric in structure, and their thickness ranges from 40 to 100 μm .²⁷ PAN or polymethyl methacrylate have a symmetric structure, whereas polysulfone or polyamide are asymmetric. The synthetic membranes are hydrophobic, allowing passage of molecules from 10 to 30,000 daltons.²⁷ This pore size allows a high rate

of ultrafiltration under relatively small pressures. These membranes have high sieving coefficient/saturation coefficients (Sc/Sd) for solutes in a wide range of molecular weights (0 to 20,000 daltons), which further contributes to high drug and metabolite clearance.²⁷ Electric charge also influences adsorption of drugs and antibiotics; PAN has a negative charge.

The surface area of the PAN filter is 0.6 m², polyamide is 0.9 m², and polysulfone ranges from 0.8 to 2.2 m². The level of adsorption by PAN filters is significantly greater than that by polyamide filters. Adsorption of both medications and toxic substances such as myoglobin onto filters in CVVH may result in significant improvements in elimination in addition to pure convective clearance. In a study that looked at amikacin dosing using PAN versus polyamide filters, the adsorption of amikacin by hemofilters was found to be irreversible and was associated with the dose of the antibiotic and the hemofilter material, but not the hemofilter surface area.²⁸ The adsorptive capacity of a filter can have a significant effect on clearance of substances, can be associated with shortened filter life, and require more frequent filter changes as the filter will become clogged after a period of significant adsorption.

THE FINAL STEP: ANTICOAGULATION

As in any extracorporeal circuit (cardiac bypass, ECMO), blood will clot in a CRRT circuit. CRRT circuits, therefore, typically require some anticoagulation. The goal in this case is to anticoagulate only the circuit while not anticoagulating the patient. In practice, the patient is always affected to some degree, but it is the goal to minimize anticoagulation of blood in the patient.

To anticoagulate the circuit, but not the patient, anticoagulant is infused after blood is removed from the patient but before entering the CRRT pump (prefilter). Prefilter measurements should be taken to ensure adequate anticoagulation of the CRRT circuit, and postfilter measurements from either the postfilter circuit or the patient must be taken to ensure minimal effect on the patient or, in the case of some anticoagulants, to counteract their effects once back in the patient.

The most common anticoagulant used is heparin. To measure the effectiveness of heparin and for dosing guidance, a prefilter and postfilter (or patient) partial thromboplastin time (PTT) should be checked. Figure 30-7 shows a complete CRRT circuit with prefilter SF using heparin as the anticoagulant. Protocols should be instituted to allow the nurse running the CRRT to adjust the heparin independently based on the measured prefilter and postfilter/patient PTT or activated clotting time (ACT). There are, however, several obvious potential contraindications to heparin. If a patient has or develops heparin-induced thrombocytopenia (HIT) or an allergy to heparin, then heparin can no longer be used. Similarly, if a patient is bleeding or has a risk of bleeding, such as trauma or recent surgery, other anticoagulants may be considered.

The next most common anticoagulant is trisodium citrate (TSC). Like the citrate added to stored blood to prevent clotting, the citrate in TSC chelates calcium, preventing activation of platelet adenosine diphosphate (ADP), thereby inhibiting

platelet aggregation and initiation of the clotting cascade.²⁹ As with all anticoagulants in CRRT, the TSC should be added to the blood draw line (i.e., as it comes out of the patient) in order to ensure anticoagulation of the entire CRRT circuit. When using TSC, it is essential that the calcium level be restored within the patient to prevent systemic hypocalcemia. Systemic anticoagulation of the patient will be prevented if the patient's ionized calcium (iCa^{2+}) level is maintained at normal levels.²⁹ Therefore, a calcium infusion must also be given concurrently. Similar to checking the PTT with the use of heparin, the filter and the patient's iCa^{2+} should be checked, and the TSC and calcium infusion adjusted accordingly. Protocols should be instituted to allow the nurse to titrate the TSC and calcium infusion independently. Note that a calcium infusion (usually calcium chloride) requires a central venous line. Furthermore, calcium is compatible with few other medications or infusions, therefore, frequently requires its own dedicated central venous port.

There are two significant potential disadvantages to TSC. First, for every molecule of citrate, there are three molecules of sodium, which may result in hypernatremia if solute balance is not carefully monitored. Utilizing a low-sodium SF can compensate to some degree, but many patients will still become hypernatremic, requiring careful monitoring. Second, the liver will metabolize the citrate in TSC to bicarbonate, which can cause a metabolic alkalosis. In that case, the TSC drip should be adjusted as well as the SF to compensate for the metabolic derangement or should be switched to another anticoagulant if this cannot be effectively managed with SF or dialysate manipulation.

There are other less commonly used anticoagulants. These include hirudin, argatroban, bivalirudin, and others. In fact, if a patient is not able to tolerate any anticoagulant, the circuit can even be run with high blood flows, high prefilter SF flow rates, varying pre- and postfilter SF percentages other than 50/50%, or frequent saline flushes to attempt to minimize clotting.

SPECIAL SITUATIONS IN WHICH ANTICOAGULATION IS NOT REQUIRED

There are a few instances in which patients do not require separate anticoagulation for the CRRT circuit. This is the case for patients who are receiving systemic anticoagulation for another indication. Therefore, dedicated anticoagulation of the CRRT circuit is not necessary. There have been no dedicated studies on the topic of patients who require anticoagulation for reasons other than the CRRT circuit (e.g., thromboembolism, atrial fibrillation, mechanical heart valve), but in these patients it is probably not necessary to run separate anticoagulation for the CRRT circuit. In these cases, it seems reasonable to simply administer systemic anticoagulation as you would for a patient who is not on CRRT. If the patient has bleeding complications from this approach and it becomes necessary to stop systemic anticoagulation, one must revert to anticoagulating the circuit in such a way as to

not affect the patient. Additionally, many critically ill patients may be coagulopathic and the one singular advantage may be the ability to run CRRT without anticoagulation.

INITIATING CRRT

After the choice has been made to initiate CRRT, the modality, filtration rate, blood flow rate, and solutions must be considered. The modality should be chosen based on goals of therapy. In CVVH, small and middle-sized molecules such as urea, creatinine, and amino acids can be removed using convection while solutes are cleared via solute drag. The addition of a given SF and its content also greatly influences serum solute concentrations. It can be chosen for standard solute removal, electrolyte imbalance, and metabolic derangement correction by manipulating the QB, QSF, substitution fluid choice, and PFR.

CVVHD is effective for small to medium-sized molecule removal, and dialysis promotes diffusion of specific molecules. It provides solute clearance, without any significant clearance of small and middle-sized molecules such as toxins or drugs. It is also useful for reversing acidosis.

CVVHDF combines hemodialysis and hemofiltration, and low-molecular-weight proteins (5000–50,000 d) such as inflammatory mediators are cleared by both convection and adsorption.³⁰

The dose of RRT, whether via IHD or CRRT, to be delivered should be prescribed before starting each session of RRT.⁵ KDIGO recommends frequent assessment of the actual delivered dose in order to adjust the prescription. The modality and prescription of RRT should achieve the goals of electrolyte, acid–base, solute, and fluid balance that will meet the patient's needs. The efficacy of a prescribed dosage of CRRT can be calculated; $K (\text{clearance}) \times t (\text{dialysis time}) / V (\text{volume of distribution})$. A volume of 3.9 L per week should be delivered when using intermittent or extended RRT in AKI. An effluent or ultrafiltrate volume of 20 to 25 mL/kg/h for CRRT in AKI is recommended. The prescribed effluent or UF volume and the actual achieved effluent or UF volume may not be the same due to interruptions in treatment such as clotting filter, interruptions of treatment, surgeries, imaging, and others. Therefore, it may be necessary to prescribe higher doses such as 30 mL/kg/h.⁵ Prescription of an effective filtration fraction (FF) in CRRT is important to maximize efficiency. The FF is equivalent to the UF divided by the plasma flow rate (Qp) ($FF = Q_{UF}/Q_p$). Plasma flow rate (PFR) is equivalent to Qb multiplied by 1 minus hematocrit (hct) divided by 100 ($Q_p = Q_b \times (1 - \text{hct}/100)$). In practice, though, often the Qb is used without the adjustment for hematocrit. The total QUF is equivalent to the PFR plus substitution fluid flow rate (QSF). For maximal efficiency and prevention of filter clotting, FF should not exceed 20% to 30%. The normal FF of a functioning kidney is 20%, which is equal to GFR/renal plasma flow (RPF). In sepsis and for the removal of soluble inflammatory mediators, a blood flow rate of > 300 mL/min and high UF rates to maintain the FF should be utilized in addition to high cut-off hemofiltration filters.

The following is a step-by-step guide for initiating CRRT³⁰:

1. Select the CRRT modality based on the indication and goals of clearance/volume removal.
2. Determine the need for anticoagulation and order accordingly.
3. Prime the machine with 1 L of 0.9% saline \pm heparin 5000 U if using anticoagulation.
4. Select the filter type. A biocompatible membrane is recommended to prevent activation of blood components/bioincompatibility.
5. Set the blood flow rate (Qb) so that the UF/Qb (FF) ratio is less than 25.
6. If using CVVH or CVVHDF, choose the substitution fluid and set the flow rate (QSF).
7. Choose the dialysate flow rate (QD) if using CVVHD or CVVHDF.
8. Set the fluid removal rate (PFR or UF). In CVVH or CVVHDF, if no fluid is removed, the replacement is the same as the UF rate.
9. Order CRRT laboratories, including chemistry panel with sodium, chloride, blood urea nitrogen (BUN), creatinine, bicarbonate, potassium.
10. Discuss pharmacokinetics with a pharmacist or review drug manufacturer's recommendations for dosing adjustments of medications given while on CRRT.

TERMINATING RENAL SUPPORT

Just as there is a relative lack of strong evidence-based support for when and how to initiate CRRT, there is a lack of evidence guiding when to withdraw renal support. Uchino et al. reported on current practices of 54 ICUs across 23 countries.³¹ While not a prospectively derived treatment rule, they found that, by far, urine output was the best predictor of successfully weaning renal support, that is, the best indicator of recovery of renal function.^{31,32} The next best indicator was creatinine clearance, but its predictive power was far inferior to that of urine output. Some intensivists wean CRRT similarly to how they would a ventilator, others just terminate therapy if the patient's renal chemical profile is improving or urine output is returning to normal.

As suggested by Gibney et al. the following criteria can be used for termination of CRRT³³:

1. Spontaneous urine output greater than 400 mL/d
2. Correction of metabolic derangements
3. No need for solute clearance
4. Stabilization of fluid balance

DIFFERENT MACHINES

Note that some machines have different terminology for the various settings. Some machines use the terms Q_B , SF, PFR, and UF, as described earlier, while some use other terminology. The take home point is that familiarity with the machine in use at your institution is of vital importance for both the

nursing staff and the prescriber. This includes knowing which settings are by convention described in milliliters per minute (Qb), which are in liters per hour (QSF), and which are in milliliters per hour (PFR and QUF). Standardized orders greatly aid this effort.

There needs to be a strong working relationship between the provider and nurses so that everyone is using the same vocabulary. All prescribers who will be evaluating or writing orders or recommendations for the therapy must be using the same terminology. This should include the intensivist, the renal consulting service, and even consulting cardiologists who will need to know the details of the patient's fluid management.

In-services should be readily available to educate staff on which machines are in use, how to set them up, and how to troubleshoot them. This should be required for all nurses and providers directly involved in running the therapy (intensivist, nephrologist) and should be made available to all others who may need to understand the therapy (e.g., cardiologist). Online modules greatly aid in this effort and, in fact, may completely suffice for the latter group.

MEDICATION DOSING

Medication dosing for patients on CRRT is beyond the scope of this text. The calculations are complex and have not been completely studied. To calculate appropriate dosing, one must take into consideration the clearance of the substance that is a function of the following items³⁴:

1. Volume of distribution of the medication, and whether a loading dose is required
2. Whether a certain medicine is cleared more by diffusion (CVVHD) or convection (CVVH)
3. What modality the patient is on: CVVH, CVVHD, and CVVHDF
4. If on CVVH, whether SF is prefilter, postfilter, or both
5. Filtration fraction
6. The sieving coefficient (how easily the medicine crosses the membrane)

Given these factors, medication dosing for these patients should involve close consultation with the pharmacology service.

SPECIAL CONSIDERATIONS: FEVER

The evaluation of fever in patients requiring CRRT is complicated by the fact that all of the modalities involve an extra-corporal circuit. Many of the CRRT machines will have an added heater to keep the blood warm, but the blood must still pass through tubing exposed to the environment. This means that the blood tubing "bleeds" heat from the patient. This heat loss may make a normothermic patient hypothermic or make a febrile patient normothermic. More important, by clearing middle molecules, such as the inflammatory mediators that produce fever, CVVH and CVVHDF (but not CVVHD) may prevent a septic patient from manifesting a fever. Thus

it would seem prudent to lower the threshold for considering a temperature elevation as a true fever, for instance, 100°F (37.8°C) instead of the more traditional 100.4°F (38°C). It would also seem prudent to send routine blood cultures at some predefined interval based on the patient's condition or local practice. There are currently no studies that define the optimal interval for routine blood cultures.

SPECIAL CONSIDERATIONS: SEPSIS

For patients with severe sepsis, CVVH holds promise as a therapy to modulate the immune response. Specifically, hemofiltration, by clearing middle-sized molecules, also clears the cytokines and other inflammatory mediators that have been implicated in the harmful immune response of sepsis. In contradistinction to solutes and fluid volume that are cleared by convection, cytokines are thought to be cleared largely by adsorption to the filter. However, since cytokines exert their influence at the tissue level, and since the filter does not remove all cytokines, it remains to be shown if clearing the cytokines truly modulates the septic response.^{35,36} Some also argue that, in clearing such cytokines, CVVH also clears the downregulating or beneficial cytokines. While true, the balance in a septic patient seems to be more toward the more harmful cytokines. Until filters can selectively remove the harmful cytokines, nonselective removal of cytokines seems a reasonable therapy. To achieve the clearance rates necessary to clear cytokines in septic shock, CVVH must be run with high SF rates and the filter must be changed at least every 6 hours when the adsorption capability of the filter declines. At that point, the filter will still clear solute, but will not remove additional cytokines. This remains one of the most promising therapies for the future treatment of septic shock. Several trials investigating the use of selective filters and filters impregnated with antibiotics such as polymyxin for hemoperfusion are ongoing.

THE FUTURE

CRRT, as "the kinder, gentler" RRT, will continue to evolve. Unlike traditional dialysis, CRRT does not require a water source and can be implemented not only in patients who are not candidates for IHD, but also in locations not set up to handle IHD. However, it is labor-intensive, requires specialized training of nurses and prescribers, and is not universally available.

As critical care moves closer to the front lines, overcrowding and ED boarding become more frequent, and early goal-directed therapy is a part of common practice, there may be instances of beneficial initiation of CRRT therapy in the ED. Emergency physicians are well versed in AKI and acute indications for dialysis. Therefore, the initiation of CRRT in the hemodynamically unstable patient while in the ED, would be an extension of current practice. Facilities must be familiar with requirements, set up, and modality options. This may include placing a large-bore, dual-lumen central line, ordering the machine, ordering the necessary fluids

(SF, anticoagulation, and so on), and rearranging staff (or calling in additional staff) to free up a nurse capable of running the CRRT machines. “Liver dialysis” is on the horizon as another feasible therapy. While not likely to be an ED therapy initially, it holds great promise for hepatic support in a number of diseases and as a bridge to a liver transplant. It draws heavily from the basics of RRT. Increasingly, the emergency physician needs to be familiar with evolving therapies, particularly when early initiation may be necessary and beneficial.

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NEUROLOGIC AND NEUROSURGICAL DISORDERS

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Alterations in Mental Status

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The human brain, then, is the most complicated organization of matter that we know.

Isaac Asimov

INTRODUCTION

The complexity of the brain renders its normal functioning—especially the production of consciousness—uniquely vulnerable to acute metabolic derangements and structural deformation. As a perpetual glucose and oxygen glutton, the brain is extremely intolerant of sudden changes in energy homeostasis, and *in vivo* neurons begin to die after only minutes of fuel deprivation. Likewise, the diffuse circuitry responsible for consciousness in the brain makes anatomic insults involving both cerebral hemispheres and the brainstem reticular activating system necessary and sufficient to perturb mental status. Regardless of etiology, altered mental status (AMS) or global cerebral dysfunction frequently prolongs hospital length of stay and worsens the prognosis of patients in the critical care setting. Rapid diagnosis is necessary to differentiate imminently life-threatening brain injury from more benign, reversible forms. As an amalgam of evidence-based practice and our clinical experience, this chapter will focus on the diagnostic and management challenges of AMS in the critically ill patient.

CONSCIOUSNESS AND THE EXAMINATION OF MENTAL STATUS

AMS is an impairment of consciousness, which is comprised of arousal and awareness.¹ Arousal refers to general brain wakefulness, while awareness defines whether the individual has knowledge of his or her own existence and surroundings. Awareness demands a certain degree of arousal but it may be dissociated, as is best exemplified by the persistent vegetative state (PVS)—awake patients without clinically demonstrable self-awareness.²

Mental status forms the core of any neurologic examination. Providers should avoid labeling a patient “unresponsive” in favor of more descriptive categories based on the physical examination: lethargy, obtundation, stupor, and coma (Table 31-1).^{3,4} Lethargic patients manifest decreased alertness but retain awareness of their environment. Obtunded patients require a stimulus to rouse and follow simple commands but have lost awareness of their immediate surroundings. Stuporous patients do not follow commands and require a continuous painful stimulus to exhibit signs of arousal. Finally, comatose patients exhibit no awareness and no significant arousal response to even painful stimuli. Coma results from bilateral cerebral hemisphere impairment or dysfunction of the reticular activating system in the brainstem; unilateral hemispheric disease (such as a middle cerebral artery stroke) does not typically

**TABLE 31-1: Descriptive Categories of Altered Mental Status**

Cloudy consciousness	A deficit in information processing by the brain exhibited by inattention; can be seen after mild to moderate brain injury and may persist for several months. Recent memory may be diminished, but long-term memory remains intact
Lethargy	A decrease in alertness, resulting in impaired ability to perform tasks normally accomplished without effort. Patients rouse briefly in response to stimuli and then settle back to inactivity when left alone. They retain awareness of their immediate environment
Obtundation	A decrease in awareness and alertness when stimulated. Patients rouse slowly in response to stimuli and follow simple commands but are unaware of their immediate surroundings. Following arousal, they settle back to inactivity
Stupor	A state in which the patient can only be aroused by continued noxious stimulation but does not interact meaningfully. Arousal may manifest only as withdrawal from painful stimuli. As soon as the stimulus is removed, the patient settles back to inactivity
Coma	A state in which the patient does not respond to the most vigorous stimuli

lead to coma unless there is associated midline shift and resultant contralateral hemispheric dysfunction. Although these categories are useful to help qualitatively describe the level of depressed consciousness in a patient, the lack of standardized definitions for these terms makes them prone to misuse and variable interpretation.

The Glasgow Coma Scale (GCS) remains one of the most important quantitative barometers for mental status (Table 31-2). Although originally designed by neurosurgeons in 1974 to classify patients with traumatic brain injury (TBI), the GCS has become a common language among acute care providers and has stood the test of time due to its ease of use, minimal interobserver variability, and prognostic capability.⁵⁻⁷ GCS is no longer solely a TBI tool, and its predictive value has been demonstrated in other diagnoses such as intracerebral hemorrhage, subarachnoid hemorrhage, intracranial subdural hematoma, ischemic stroke, Alzheimer's dementia, and poisoning.⁸⁻¹³

The GCS is composed of a motor, verbal, and eye opening score; however, some studies have suggested that the most

useful (because it can be performed on intubated patients) and predictive component of the GCS is the motor score.^{14,15} Moreover, in addition to its limited utility in intubated patients (in which the verbal score is replaced by "T"), the GCS has often been criticized for failing to include brainstem reflexes.¹⁶ Nevertheless, the GCS remains the reigning worldwide consciousness scale and continues to facilitate both clinical research and decision making.

The motor component of the GCS deserves particular attention because it contains the most information and typically requires the most practice and effort to confidently extract from the physical examination. To meet the criteria of following commands, we recommend that the patient must show two fingers or wiggle his or her thumb to a verbal command. A common pitfall occurs in aphasic patients, who may mimic the examiner if given a visual cue and therefore make it seem as though commands are being followed. Similarly, we recommend strict criteria for determining localizing, wherein the patient exhibits both cranial and caudal localization of the stimulus. Finally, withdrawal should be recognized as being a fairly complex and nonstereotypical movement of an extremity away from a painful stimulus; it must be distinguished from the simpler posturing flexion and extension movements.

The Full Outline of UnResponsiveness (FOUR) score is an alternate coma scale that provides greater detail of brainstem reflexes and respiratory patterns. It consists of four elements (eye, motor, brainstem, and reflexes), and each component has a maximal score of 4 (Table 31-3). When compared with the GCS, the FOUR score has similar interrater reliability, predictive value of mortality, and can be used across a diversity of critically ill neurological patients.^{17,18} While the FOUR score provides more neurological detail than the GCS, neither scales should replace a thorough neurological exam.

**TABLE 31-2: Glasgow Coma Scale (GCS)****Eye opening**

Spontaneous	4
To voice	3
To pain	2
None	1

Verbal response

Oriented	5
Confused	4
Inappropriate	3
Incomprehensible	2
None	1

Motor response

Follows commands	6
Localizes to pain	5
Withdraws to pain	4
Flexion to pain	3
Extension to pain	2
None	1

DIFFERENTIAL DIAGNOSIS OF ALTERED MENTAL STATUS

Although there are myriad causes of AMS in the ICU, the basic dichotomy in global cerebral dysfunction is whether it has been anatomically or metabolically engendered. Clinical acumen gives the physician a general gestalt as to what type of cognitive reserve one can expect in a patient. Cognitive



TABLE 31-3: Full Outline of UnResponsiveness (FOUR) Score

Eye response	
Open, tracking or blinking to command	4
Open but not tracking	3
Closed but opens to loud voice	2
Closed but opens to pain	1
Remains closed with pain	0
Motor response	
Thumbs up, fist, or peace sign to command	4
Localizing to pain	3
Flexion response to pain	2
Extensor posturing	1
No response to pain or generalized myoclonus	0
Brainstem response	
Pupil and corneal reflexes present	4
One pupil wide and fixed	3
Pupil <i>or</i> corneal reflexes absent	2
Pupil <i>and</i> corneal reflexes absent	1
Absent pupil, corneal, and gag reflex	0
Respiration	
Not intubated, regular breathing pattern	4
Not intubated, Cheyne-Stokes breathing pattern	3
Not intubated, irregular breathing pattern	2
Breathes above ventilator rate	1
Breathes at ventilator rate or apnea	0

reserve, defined as the brain's ability to resist insult, is a function of patient age, baseline brain function, brain volume, comorbidities, and perhaps duration of stay in an ICU.¹⁹ For example, one may expect that a urinary tract infection might cause obtundation in an 82-year-old woman in the ICU but would be reluctant to attribute such a cause to obtundation in a 30-year-old patient. History provided by the patient's family can aid in the diagnosis of AMS by both helping gauge cognitive reserve (e.g., by identifying baseline brain function and whether there are signs of an underlying dementia) and identifying substance abuse disorders, most notably alcohol dependence. As a good rule of thumb, anatomic causes of AMS (intracerebral hemorrhage, ischemic stroke, subarachnoid hemorrhage, cerebral venous sinus thrombosis, vasospasm, hydrocephalus) tend to have a more rapid onset and tend to cause a greater decrement in GCS, although fever, hyponatremia, and septic encephalopathy are becoming more recognized as important contributors of morbidity and mortality.

Pupil size and light reactivity and motor exam symmetry are typically preserved in metabolic encephalopathy. Even in the presence of nondepolarizing neuromuscular blockade when motor exam has been lost, pupil reactivity is typically preserved.²⁰ Dilation of a pupil with loss of light reactivity heralds third cranial nerve compression with very few exceptions; rarely, seizure may cause this same response.²¹ Prospective studies have confirmed that both anisocoria and loss of the pupillary light reflex have high positive predictive values

for structural coma.²² Extremely small symmetric and reactive pupils may be caused by a pontine lesion. Moreover, metabolic encephalopathy may amplify or accentuate a pre-existing motor asymmetry (e.g., an old hemiparesis from stroke may become more pronounced in the presence of hyponatremia) but rarely manifests with a new motor exam asymmetry. Recalling the brain's appetite for glucose, hypoglycemia is one cause of metabolic encephalopathy and rapid-onset coma that may cause a focal neurologic deficit along with AMS; glucose determination must accompany any acute evaluation of AMS since hypoglycemic episodes in diabetics have not uncommonly been misdiagnosed as strokes.^{23,24}

The prevalence of etiologies for AMS in the ICU undoubtedly depends on the type of unit. Multiple studies have shown that AMS prolongs hospital stay and is an independent risk factor for mortality in the ICU.²⁵⁻²⁹ In one study of 1,758 patients admitted to a medical ICU for a non-neurologic reason, metabolic encephalopathy was found to be the primary cause of AMS, followed by seizures; among the metabolic encephalopathies, septic encephalopathy was the leading culprit, followed by hepatic and renal encephalopathies.³⁰

In another study involving patients in a medical ICU, Isensee et al. reported that metabolic encephalopathy was the most frequent cause of AMS, and those patients with AMS had more than double the mortality rate seen in patients without AMS.³¹

SEPTIC ENCEPHALOPATHY

Septic encephalopathy is a leading cause of AMS in the critical care setting; however, the exact pathogenesis for global cerebral dysfunction in sepsis remains unknown. It is likely that the process is multi-factorial and patient specific. As a neurophysiologic indicator of global cerebral dysfunction, abnormal evoked potentials were found in 84% of septic ICU patients in one study.³² Recent studies using mouse models of lipopolysaccharide-induced encephalopathy have suggested that the cytokine tumor necrosis factor (TNF) plays an important role in initiating and maintaining an inflammatory state in the brain.³³ Brain microabscesses, abnormal amino acid metabolism, changes in brain neurotransmitter concentrations, reduced cerebral blood flow and oxygen utilization, and weakening of the blood-brain barrier with resultant cerebral edema have all been implicated in the pathogenesis of septic encephalopathy.³⁴⁻³⁷ Cerebrospinal fluid analysis is normal or with mild protein elevation, and electroencephalogram (EEG), the most sensitive test for septic encephalopathy, usually demonstrates a pattern consistent with metabolic encephalopathy with diffuse slow waves (predominantly delta waves) often with a triphasic pattern. Rarely, septic encephalopathy may manifest with focal neurologic deficits in addition to AMS.³⁸ Regardless of the causes, sepsis in the ICU causes acute AMS and may often leave patients with long-term cognitive morbidity. Animal models are helping to pave the way toward therapies that might counter the pathophysiologic mechanisms behind brain failure in sepsis; however, at present, our only defense is early identification and treatment

of infection with a high index of suspicion for concomitant neurological insults.

NONCONVULSIVE STATUS EPILEPTICUS

There are few epidemiologic data on seizures in critical care; however, even one seizure in an adult ICU patient may double mortality.²⁸ While the management of isolated partial or generalized seizures and status epilepticus is generally well known among intensivists, much less attention has been granted to subclinical seizures and nonconvulsive status epilepticus (NCSE). There is no current international EEG-based definition or classification scheme for NCSE. NCSE has been defined as AMS associated with continuous epileptiform changes on EEG in the absence of motor signs.³⁹ Unfortunately, the diagnosis of NCSE is further hampered by a lack of a pathognomonic EEG pattern. NCSE may be focal or generalized based on EEG that most commonly shows spike-and-wave or polyspike-and-wave discharges (usually with frequency < 2–3 Hz); some have divided the EEG patterns in NCSE into five categories: continuous focal spike and wave, continuous generalized spike and wave, continuous generalized sharp and wave, continuous focal sharp and wave, and continuous periodic lateralized epileptiform discharges.⁴⁰ The prevalence of NCSE in patients with coma has been estimated to be as high as 3–8%; this is likely underestimated because the more commonly utilized routine EEG (20–30 minutes) is less sensitive for convulsive and nonconvulsive epileptic activity than is continuous EEG.⁴¹ The diagnosis of NSCE is therefore often missed, and this has been

a frequent argument among proponents of continuous EEG monitoring in the ICU; NCSE, independent of etiology, worsens patient morbidity and mortality.^{42,43} Current treatment for NCSE involves prescribing benzodiazepines (especially lorazepam and midazolam), antiepileptics (phenytoin, levetiracetam, fosphenytoin, valproate, and phenobarbital), and intravenous anesthetics such as propofol and ketamine with a goal of suppressing EEG abnormalities.⁴⁴

LOCKED-IN SYNDROME

Locked-in syndrome (LIS) is the constellation of anarthria, quadriplegia, and horizontal gaze paresis caused most commonly by an ischemic insult to the ventral pons⁴⁵ (Figure 31-1). Patients with LIS can communicate solely with blinking and vertical eye movements. LIS is not a disorder of consciousness but can easily be misconstrued as coma since there is a near complete deprivation of voluntary activity. Especially in patients with brainstem pathology, physicians must remember to assess for vertical eye motion prior to declaring a patient comatose. While still a grave diagnosis, LIS needs to be identified and distinguished from coma because there may be a counterintuitive potential for good recovery with supportive care and aggressive rehabilitation.⁴⁶

PERSISTENT VEGETATIVE STATE AND MINIMALLY CONSCIOUS STATE

Brought to the public eye by recent cases covered by the lay press, PVS is a form of AMS in which there is preserved alertness, sleep–wake cycles, and autonomic control but absent

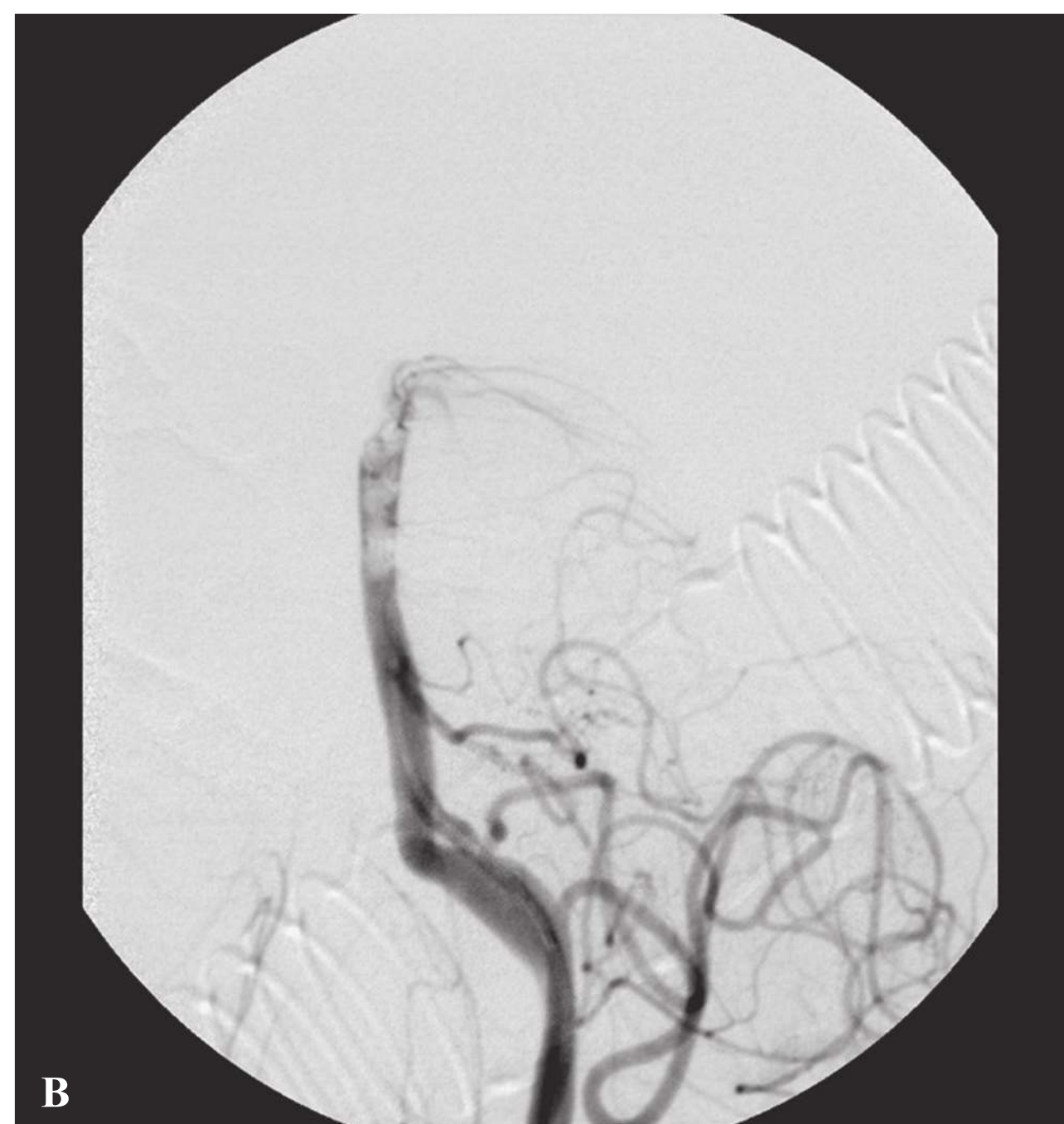
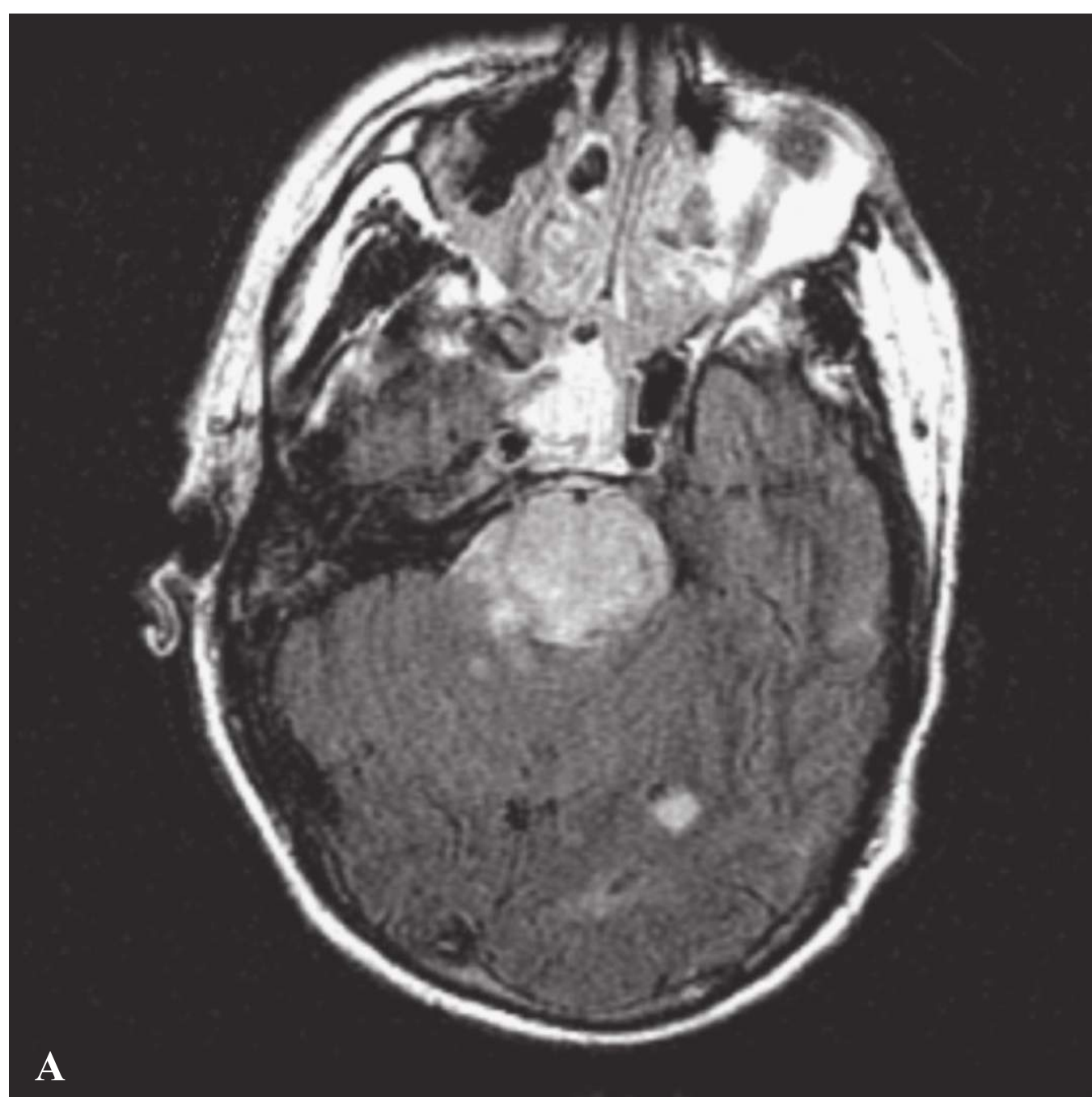


FIGURE 31-1 Locked-in syndrome. Axial FLAIR sequence MRI of the brain demonstrating a massive pontine infarction in a 46-year-old man with locked-in syndrome secondary to basilar artery thrombosis (**A**). Cerebral angiography demonstrating thrombus in the distal basilar artery (**B**).

awareness and only reflexive movements.⁴⁷ If such patients exhibit some nonreflexive movements as well, they are classified as being in a minimally conscious state (MCS). The PVS and MCS may develop as patients recover from coma. Head trauma with diffuse axonal injury and anoxia are the major brain insults that engender the PVS. Neuroimaging tools such as functional magnetic resonance imaging (fMRI) have reinvigorated ethical debates concerning the PVS by demonstrating that these patients may retain some component of conscious awareness.⁴⁸ Nevertheless, the PVS remains a devastating diagnosis and reversibility is rare. Emerging technologies such as deep brain stimulation offer the potential of augmenting consciousness in these patients.⁴⁹

CEREBRAL ISCHEMIA AND BRAIN DEATH

In vitro studies have shown that central nervous system neurons can tolerate between 20 and 60 minutes of complete ischemic anoxia without irreversible injury.⁵⁰ However, the injury in vivo is much more severe and occurs in much less time. Immediately after cessation of circulation to the brain, the cerebral vessels dilate in response to the local environmental factors and increased $Paco_2$. Because the brain has no stores of glucose, cellular metabolism quickly ceases. Loss of nutrients and hypoxia cause the most sensitive structures to lose cellular integrity. This results in leakage from capillaries, edema, and disruption of cells and leads to release of lysosomes, proteases, and other damaging compounds into the surrounding tissues.⁵¹ This in turn results in clogged microcirculation, stasis, and a vicious circle of increasing damage backing up into the macrocirculation. If this process is allowed to continue for a variable length of time and blood flow is then reestablished, the increased pressure gradient in the damaged area tends to disrupt the architecture, much like the sudden bursting of the Hoover Dam might do to downstream communities. The result is a progressive postresuscitative hypoperfusion state, in which blood flow is decreased to below the 20% level within 90 minutes postreperfusion and remains at this low level for up to 18 hours.^{52,53}

Two theories have been offered to explain these phenomena: (1) Massive calcium (Ca^{2+}) overloading of the cells may be the initial stage of irreversible damage.⁵⁴ Normally, the extracellular Ca^{2+} level is high and the intracellular level is low. The damage of the cell membrane from hypoxia and loss of nutrient flow allows the gradient to shift and Ca^{2+} to enter the cell, causing interference with enzymes, DNA, RNA, mitochondria, and energy production cycles. Infusion of high levels of Ca^{2+} into precapillary arterioles causes vasospasm and a vicious cycle of decreased flow, more depletion of oxygen and nutrients, and so on. (2) During ischemia, oxygen-free radicals may be created by abnormal metabolism. These free radicals attack DNA, RNA, and mitochondria, resulting in irreversible damage.⁵⁵

As it pertains to brain death in the United States, philosophical ruminations on the meaning of life and death are fortuitously muffled by state law.⁵⁶ Brain death is a legal death

that is relatively resistant to interpretation.⁵⁷ The brain death exam basically interrogates the brainstem at normal body temperature and in the absence of drugs that can suppress the central nervous system or the neuromuscular junction. It is a diagnosis of what is, not what might be.⁵⁸ Simply put, brain death equals legal death. The concept of brain death is relatively new and exists due to development of life support devices such as mechanical ventilation and is important due to the development of organ transplantation. Once objective criteria are met on physical examination, a physician can pronounce a patient brain dead; some states require more than one physician to make this pronouncement. The family is informed that the patient has died. If the patient is not a candidate for organ donation, life support will be removed, and a death certificate is issued in the same manner as in any other death. If the patient is a potential organ donor, a death certificate will be issued and the state's organ procurement organization will manage the organ donor until the time of organ donation. Overall, the criteria behind brain death are similar worldwide. Brain death is clinically determined and usually is diagnosed by examination. In some circumstances, additional tests are used and will be outlined later in this section.

A brief summary of a typical brain death protocol is presented here.^{59,60}

The cause of injury must be known. There must be clear evidence of an acute, catastrophic, irreversible brain injury. This is extremely important. There must be clear, objective evidence of brain injury on computed tomography (CT) or MRI of the brain that is compatible with the physical exam. A physical exam compatible with brain death is by itself insufficient, as numerous tabloid media sources routinely proclaim when supposed brain dead patients unexpectedly awaken.

Reversible conditions that may confuse the clinical diagnosis of brain death must be excluded, including:

- Hypothermia; body temperature must be $> 36^{\circ}C$
- Drug intoxication or inadvertent neuromuscular blockade
- Hypoperfusion and shock; systolic blood pressure must be ≥ 100 mm Hg

The physical examination:

- No response to verbal or visual command
- No musculoskeletal movements to pain
- Pupils fixed and nonreactive
- No corneal reflex
- No oculoccephalic reflex
- Negative oculovestibular reflex
- No gag or cough reflex
- No spontaneous ventilation

The apnea test: This test should be the last test and should be conducted after the clinical exam has confirmed the absence of brainstem function. The patient is disconnected from the ventilator while oxygenation of the lungs continues passively. By calculation ($Paco_2$ rises 4 Torr in the first minute and 3 Torr every minute thereafter), the patient is allowed to build up to a $Paco_2$ of 60 Torr or more without becoming hypoxic. If there is no respiratory effort, the test is considered confirmatory.⁶¹

The EEG: An EEG is not necessary for confirmation of brain death because small artifacts may confuse the issue. For this reason, many authorities argue that EEG should not be ordered in a person suspected of brain death. If ordered, the EEG should show electrocerebral silence for at least 30 minutes and must conform to established criteria for brain death.⁶²

When the cause of death cannot be determined without absolute accuracy, consider cerebral angiography or cerebral scintigraphy (nuclear medicine study). The absence of intracranial arterial circulation as demonstrated by four-vessel angiography or radionuclide in the cerebral hemispheres confirms brain death.⁶³

Often, two separate clinical examinations are done, one by a neurologist or neurosurgeon and the other by a critical care specialist, before performing the apnea test or a confirmatory test. However, some institutions allow a single exam. If, after this extensive clinical examination, the patient shows no sign of neurologic function and the cause of the injury is known, the patient can be pronounced dead (by neurologic criteria) and a death certificate is completed with the time of death noted as the time the protocol was completed.

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Management of Acute Intracranial Hypertension

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The cranial vault is a rigid structure containing brain, blood, and cerebrospinal fluid (CSF). According to the Monroe–Kellie doctrine, the volume of this chamber is unchangeable, and any addition of contents must be matched by a displacement of volume elsewhere. The goal of this chapter is to briefly outline the pathophysiologic processes that result in volume shifts in the cranium and measures that can be taken to identify and treat these conditions.

WHAT IS INTRACRANIAL PRESSURE?

Intracranial pressure (ICP) is defined as the pressure exerted on the dura mater by the intracranial contents.¹ It comprises the sum of three partial pressures:

$$ICP = P_{\text{Cerebrum}} + P_{\text{Blood}} + P_{\text{CSF}}$$

Any increase in the partial pressure of one compartment will cause a decrease in the pressure of another to maintain a constant ICP. The change in volume divided by a change in ICP is defined as intracranial compliance. Initially, the addition of volume is easily accommodated in the vault without a corresponding increase in pressure. Once this “compensatory reserve”² is exhausted, the pressure rises rapidly in response to an increase in volume (Figure 32-1).

Normal ICP ranges between 5 and 15 mm Hg or 7.5 and 20 cm H₂O.³

An increase in ICP can jeopardize the cerebral perfusion pressure (CPP) that is defined as:

$$CPP = MAP - ICP$$

where MAP is the mean arterial pressure, and hence the cerebral blood flow (CBF) = CPP/cerebral vascular resistance (CVR).

Although transient ICP elevations of up to 100 mm Hg have been tolerated by the human brain under experimental conditions,⁴ sustained ICP values above 20 mm Hg are associated with worse outcomes in brain trauma patients. CPP is less predictive of neurologic outcome as long as it is maintained above 60 mm Hg.⁵

CEREBRAL AUTOREGULATION

In normal physiologic states, CBF remains stable or “autoregulated” over a wide range of CPP through cerebral arteriolar vasodilation and vasoconstriction.⁶ CPP and ICP are clinical surrogates for CBF and therefore are utilized as clinical diagnostic and therapeutic indices. CVR is increased or decreased based on alterations in CPP when autoregulation is intact. As CBF decreases beyond the limits of autoregulation, the brain increases its oxygen extraction fraction (OEF) to compensate for reduced blood flow. In the neurologically injured brain, the concept of autoregulation may be disrupted, and therefore the normal compensatory measures may not exist. Any

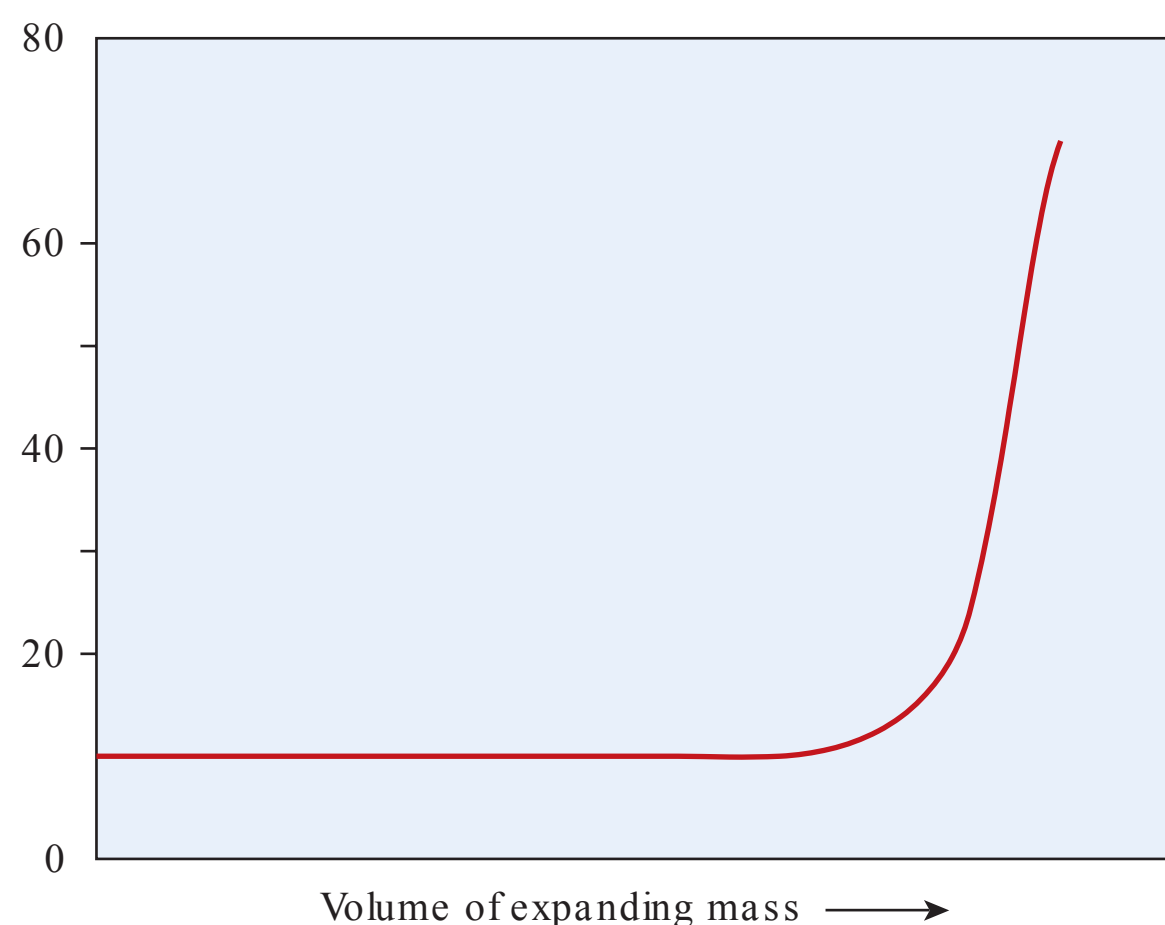


FIGURE 32-1 The pressure–volume curve: Until a certain point, the skull can accommodate volume without a significant change in pressure. Beyond this, any increase in volume is associated with a disproportional increase in intracranial pressure.

therapeutic measures directed toward improving the injured brain or other organ systems should consider this pathophysiologic process/concept prior to instituting therapy.

CLINICAL SIGNS OF INTRACRANIAL HYPERTENSION

The clinical presentation of elevated ICP depends on the etiology and varies in reliability. Signs include somnolence, papilledema, a symptom complex of headache, nausea/vomiting, and blurry/double vision, or a complex of bradycardia, irregular respirations, and widened pulse pressure (Cushing's triad).⁷ Cushing proposed that these findings in the presence of profound intracranial hypertension were a sign of medullary ischemia. However, this constellation can be seen anytime there is distortion of the brainstem even in the setting of normal ICP⁸ and should be considered an ominous trend without a specific clinical correlation to intracranial hypertension.

Acute increases in ICP, such as those due to epidural hematomas, subarachnoid hemorrhage (SAH), or severe brain trauma, usually present with a more global impairment in cerebral function such as low Glasgow Coma Scale (GCS) score, headache, nausea, and vomiting. Venous bleeds, subdural hematomas, brain tumors, and malignant strokes are more likely to present as focal neurologic deficits progressing to one of the herniation syndromes and elevated ICP. In these patients, it is important to monitor for worsening paresis, cranial nerve palsies (especially third and sixth nerves), and pupillary changes.

RADIOGRAPHIC SIGNS OF INTRACRANIAL HYPERTENSION

Any patient with suspected intracranial hypertension should undergo emergent neuroimaging. Concerning findings include:

- Presence of acute intraventricular, subarachnoid, epidural, or subdural blood

- Obliteration of the third ventricle or basal cisterns⁹
- Dilation of the contralateral temporal horn¹⁰
- Obstructive hydrocephalus with enlarged lateral ventricles and transependymal flow³
- Midline shift
- Diffuse or focal cerebral edema—loss of gray–white junction, large-vessel ischemia, or large areas of vasogenic edema resulting in sulcal effacement

HERNIATION SYNDROMES

The shifting of intracranial contents from one intracranial compartment to the next because of mass effect is called herniation.¹¹ There are different types of herniation syndromes: (1) transtentorial herniation, (2) central herniation, (3) tonsillar herniation, and (4) subfalcine herniation (Figure 32-2).

INDICATIONS FOR ICP MONITORING

ICP should be measured whenever elevation of ICP is suspected in patients who will benefit from the procedure. There is insufficient level I evidence to support a standard for ICP monitoring or to confirm that it improves outcomes. According to the most recent traumatic brain injury (TBI)

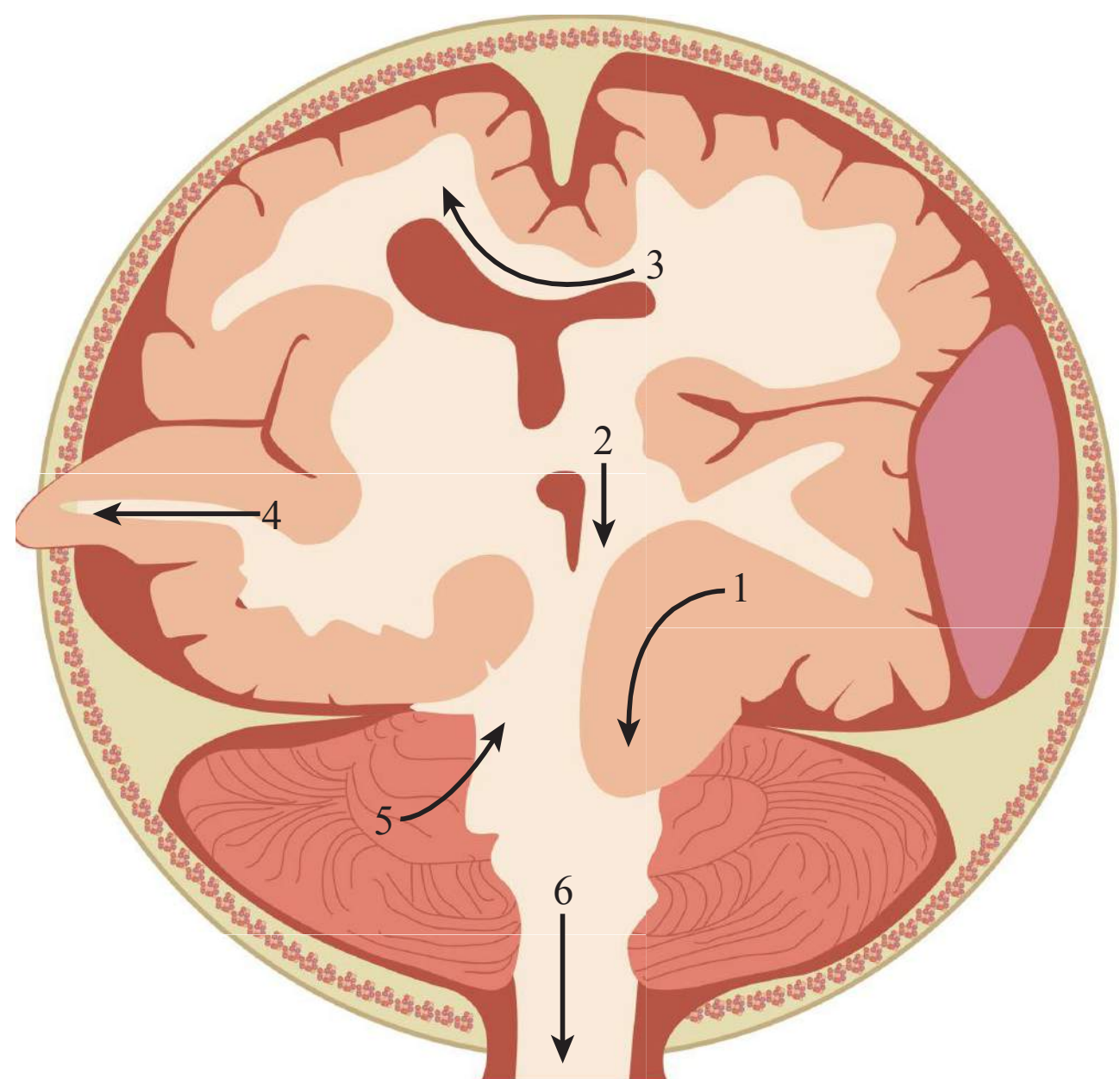


FIGURE 32-2 Herniation syndromes: (1) uncal herniation can result in third cranial nerve, posterior cerebral artery, and midbrain compression; (2) central herniation can cause downward displacement of the entire brainstem with lateral gaze palsy; (3) subfalcine herniation can result in strangulation of the anterior cerebral artery under the falx; (4) extracranial herniation can occur through a traumatic skull defect or therapeutic craniectomy; (5) upward tentorial herniation can occur due to posterior fossa masses; (6) tonsillar herniation can result in brainstem compression, pupillary dilation, and cardiorespiratory arrest.

guidelines,¹² there is level II evidence that all salvageable patients with a GCS score of 3–8 and an abnormal computed tomography (CT) scan should have some form of ICP monitoring. Level III evidence supports ICP monitoring in all patients with severe TBI and a normal CT who have two of the following: age > 40 years, unilateral or bilateral motor posturing, or a systolic blood pressure < 90 mm Hg. Beyond these guidelines, indications are less well defined, although ICP monitoring is used in poor-grade SAH, intraventricular hemorrhage, intraparenchymal hemorrhage, meningitis, acute liver failure, hydrocephalus, and the like.

In 2012, a controversial publication by Chestnut et al.,¹³ performed in developing countries in patients who received delayed and unstandardized prehospital care, suggested that there was no difference in survival or functional status in severe TBI patients undergoing pressure-guided ICP management compared to that based on clinical and imaging findings alone. The study has been widely criticized for its inability to address ethical and systemwide issues, and its findings have not been incorporated into standard practice in developed countries.

MEASUREMENT OF INTRACRANIAL PRESSURE

The gold standard for ICP monitoring is direct measurement in the lateral ventricle (Figure 32-3). This allows for continuous monitoring of the ICP and CSF drainage for ICP control. External ventricular drains (EVDs) are inserted into the ventricle through a burr hole. They are connected to a transducer and a drainage bag, which is positioned at a set level above the tragus to maintain the desired ICP. It is important to remember that the height of the collecting bag relative to the tragus is often measured in centimeters of water (cm H₂O), whereas ICP is measured in millimeters of mercury (mm Hg). The biggest complications of EVDs are malfunction and infection. Infection rates from 5% to 20% have been documented in the literature¹⁴ and are related to surgical technique, duration of EVD placement, frequency

of manipulation, and catheter flushing. In general, more than three placement attempts and flushing more than twice for malfunction should be avoided.¹ Neither routine catheter exchange nor the use of prophylactic antibiotics is recommended to reduce infections.¹⁵

Intraparenchymal monitors are less invasive and independent of head position. They cannot be re-zeroed once inserted, although the newer models have less drift, making this less of an issue.¹⁶ These devices measure pressure in the anatomic compartment that they are placed in, which may not be an accurate assessment of global (ventricular) ICP.

Subarachnoid bolts are hollow saline-filled bolts that are screwed into the burr hole. The fluid in the lumen is continuous with the CSF in the subarachnoid space, and the transmitted pressure is considered the ICP. The main advantages of this device are the ease of insertion and the low risk of infection and bleeding. However, they do not allow for CSF drainage, are less accurate than EVDs, and tend to become occluded by the swollen brain.¹⁷

Epidural devices are fiberoptic catheters that are placed in the space between the skull and dura. Although they have a low risk of infection and bleeding, they are often inaccurate.

More recently, focus has shifted to noninvasive ICP monitoring techniques. Perhaps the most easily accessible of these is the ocular ultrasound. Several small studies have documented that measurement of the optic nerve sheath diameter (ONSD) 3 mm behind the globe can reliably identify patients who have evidence of elevated ICP on brain imaging.¹⁸ A correlation of ONSD to ICP assessed by an intraparenchymal probe in brain trauma patients revealed a reliable increase in diameter at ICP values > 20 mm Hg.¹⁹

MANAGEMENT OF INTRACRANIAL HYPERTENSION

Once the diagnosis of intracranial hypertension has been established, the treatment can be directed to the cause: CSF drainage for hydrocephalus, steroids and resection for intracranial tumors, and craniectomy for strokes. General principles of ICP management continue until definitive treatment can be implemented, or if the patient is not a candidate for any of the listed treatments. As with all emergencies, the airway, breathing, and circulation must be stabilized before any further steps are taken.

Position

A change in head position from 0 to 60 degrees is associated with a significant decrease in ICP²⁰ because it improves venous return and decreases CSF hydrostatic pressure. Unfortunately, this is coupled with a drop in MAP and CPP²¹ that may adversely affect patients with impaired cerebral autoregulation. A midline head position ensures that both jugular veins are open and draining. Special attention should be given to collars and endotracheal tube (ETT) holders, which may be constrictive and impair venous return.

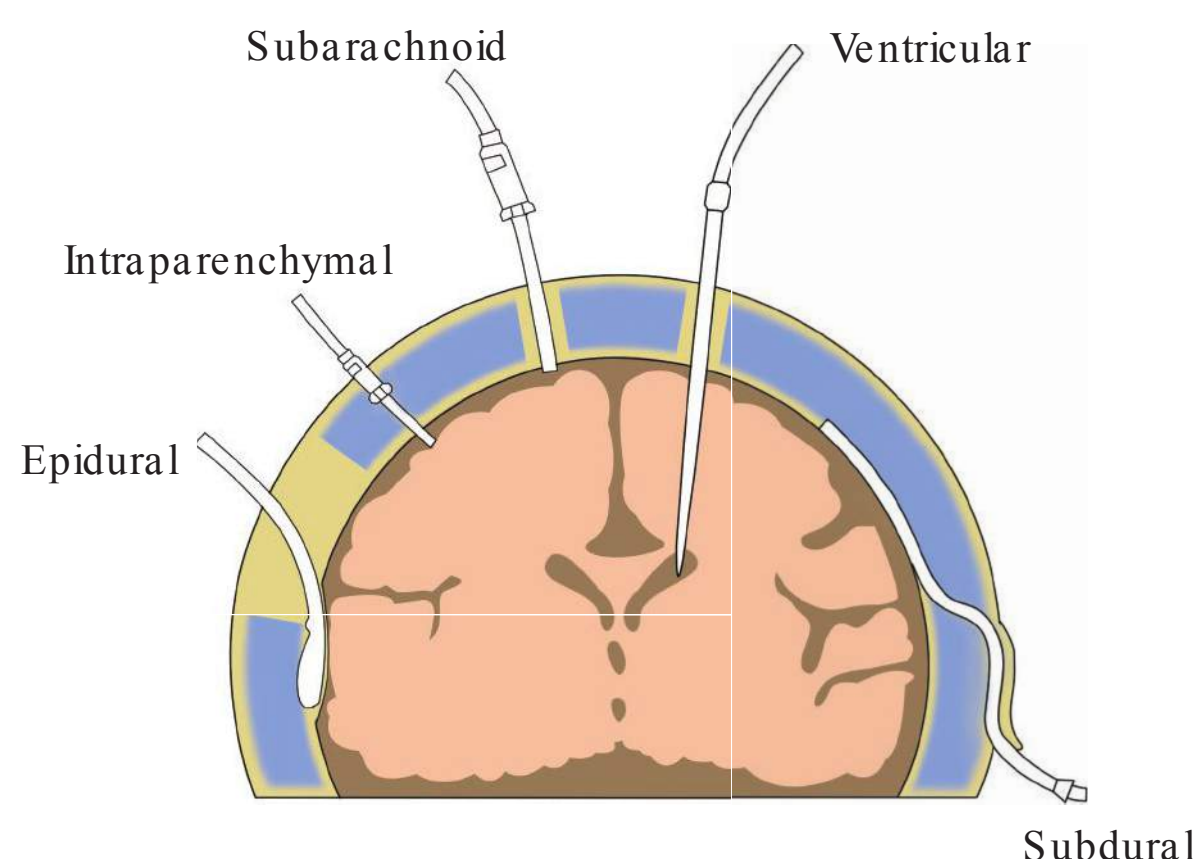


FIGURE 32-3 Location of various intracranial pressure monitors.

Hyperventilation

A decrease in P_{CO_2} effectively decreases the ICP²² by causing cerebral arteriolar constriction and reducing cerebral blood volume. The effect generally lasts for less than 24 hours, and prolonged hyperventilation should be avoided. Level II evidence discourages maintaining P_{CO_2} levels below 25 mm Hg in TBI patients given the risk for global ischemia.²³ In general, eucapnia should be maintained and hyperventilation should be avoided or only used as a temporizing measure.

Hemodynamics

As the ICP rises, the MAP reflexively increases to maintain CPP. More protocols are now incorporating CPP-targeted therapies with a lower limit of ≥ 60 mm Hg. This allows for less use of vasopressors and fewer pulmonary complications than ICP-driven management of brain injury.²⁴

Hyperosmolar Therapy

Mannitol is the most commonly used osmotic agent in the treatment of intracranial hypertension. It is usually dosed as a bolus infusion at 0.25–1.0 g/kg body weight. It does not cross the blood–brain barrier (BBB) in uninjured brain tissue but can in areas where the BBB is compromised, creating a reverse osmotic effect. Mannitol acutely expands the intravascular volume, increasing CBF. This in turn enhances oxygen delivery to the brain and causes vasoconstriction in areas of the brain where autoregulation is intact, resulting in a decrease in ICP. Mannitol also creates an osmotic gradient between the cells and plasma, resulting in reduction of intracerebral volume and a drop in ICP. There is subsequent urinary osmotic diuresis, which should be replaced by intravenous fluids to avoid dehydration, hypotension, and renal failure. These side effects are more common when the drug is dosed frequently, continuously, or in large volumes, especially at serum osmolarities > 320 mOsm.²⁵ Renal toxicity is one of the primary concerns with usage of mannitol especially when given in scheduled dosing regimens or in continuous intravenous formats. It is related to mannitol accumulation, and therefore osmolar gap should be calculated in multiple-dose formats:

$$\text{Osmolar gap} = \text{measured POsm} - \text{calculated POsm}$$

$$\text{Plasma osmolarity (POsm)} = 2[\text{Na}] + \frac{[\text{glucose}]}{18} + \frac{[\text{BUN}]}{2.8}$$

There have been no randomized controlled trials to prove mannitol's superiority over other agents or an improvement in outcomes with its use.

Hypertonic saline (HS) reduces ICP by creating a hyperosmolar gradient across the BBB. ICP reduction has been noted to last for ≤ 2 hours but may be maintained for longer with a continuous infusion.²⁶ Side effects include electrolyte abnormalities, heart failure, and phlebitis. In a recent comparison of equiosmolar mannitol and 7.5% HS, both equally reduced ICP but mannitol had the added benefit of improving CPP.

Since then, a series of patients refractory to mannitol were treated with 7.5% HS with marked reduction in ICP and improvement in brain tissue oxygen tension (PbtO_2) and cerebral and systemic hemodynamics.²⁷ Thirty- and 60-mL boluses over 15 minutes of 23.4% saline as a single osmotic agent have also been found to be safe and effective in reducing ICP and improving CPP and PbtO_2 .²⁸

Temperature

Fever has been associated with adverse outcomes in all forms of brain injury, most likely secondary to an increase in brain metabolic demands. Induced moderate hypothermia (32–34°C) has been used to reduce cerebral edema, but no definite benefit has been seen with the exception of postcardiac arrest anoxic injury. Outcomes are influenced by the depth and duration of hypothermia, as well as the rate of rewarming.²⁹ Passive rewarming of patients who were hypothermic on arrival to the hospital was associated with worse outcomes than patients who were maintained at hypothermic temperatures.³⁰ Shivering, a common side effect, elevates ICP and may require higher doses of sedation or neuromuscular blockade. Other side effects include coagulopathy, arrhythmias, and suppressed immune responses. At this time, the advantages of hypothermia as a neuroprotective agent have not been proved to be greater than the risks, and treatment should be guided toward maintenance of normothermia. Questions that need to be answered include which patient populations may benefit, if any; what degree of hypothermia; and for how long hypothermia should be maintained.

Barbiturates, Analgesia, and Paralytics

Barbiturates reduce ICP by reducing brain metabolism and therefore CBF and volume. Pentobarbital is more commonly used given its intermediate half-life (approximately 20 hours) and is usually administered as a bolus of 10–30 mg/kg followed by an infusion of 0.5–3 mg/kg/h with the goal of achieving burst suppression. Barbiturates alone are seldom sufficient for the control of ICP when compared with mannitol.³¹ Their use is fraught with multiple side effects including profound cardiac suppression, vasodilation, and immunosuppression. The hypotension and associated drop in CPP often negates any advantages of ICP control, and patients often need to be hemodynamically supported on vasopressors. The use of barbiturates should therefore be limited to patients who have elevated ICP that is refractory to standard medical and surgical management.³² Propofol has been used as an alternative to barbiturates because of its very short half-life, reduction in cerebral metabolism, and antiseizure properties.³³ Its use is limited by hypotension as well as by the fact that it is lipid solvent, which can cause severe hypertriglyceridemia and increased CO_2 production. The risk of propofol infusion syndrome, although rare, discourages many practitioners from long-term usage.

Pain, agitation, and shivering can increase cerebral metabolic demand and ICP. Patients should be on adequate doses

of opioid analgesics to avoid this. When shivering or motor posturing is intractable, neuromuscular blockade with non-depolarizing aminosteroidal agents can be used. The pharmacokinetics of these agents may be altered in the setting of hypothermia, and they should be dosed accordingly.

Decompressive Craniectomy

Removal of part of the skull for ICP control aims to negate the Monroe–Kellie doctrine of fixed volume by allowing the brain to swell out of the cranial defect.³⁴ Craniectomy has been used to treat intractable intracranial hypertension due to strokes, SAH, TBI, and intracranial hemorrhage. There is ample level I evidence supporting the use of decompression in malignant strokes.³⁵ Data for TBI were restricted to case series, until recently, when the DECRA trial investigators randomized patients with diffuse brain injury and refractory ICPs to bifrontotemporal decompressive craniectomy or standard care.³⁶ Although patients in the craniectomy group had significantly lower ICPs and shorter ICU lengths of stays, they had worse scores on the Extended Glasgow Outcome Scale in 6 months (odds ratio 1.84). Rates of death were similar at 6 months between the two groups. If surgical decompression is considered, it should be done expeditiously and generously, ideally after the first-tier treatments have failed.

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Stroke

Evie G. Marcolini

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INTRODUCTION

Stroke continues to be a major cause of morbidity and mortality in adult populations worldwide. More than 795,000 patients are diagnosed with new or recurrent stroke each year in the United States alone, and this entity is the fourth most frequent cause of death among adults, ranking behind heart disease, cancer, and chronic lower respiratory disease.¹ Ischemic stroke comprises 87% of all strokes. This disease is a leading cause of disability in the adult population. More than 50% of stroke sufferers will be left with permanent disability, 25% will require some assistance with activities of daily living, and 25% of patients will remain in an institutional setting 6 months poststroke.²

The management of acute stroke had been strictly supportive until 1995, when the National Institute of Neurological Disorders and Stroke (NINDS) rt-PA Stroke Study Group published their trial of recombinant tissue plasminogen activator (rt-PA) in the treatment of acute ischemic stroke.³ The availability of an effective therapy triggered a renewed interest in treatment of acute ischemic infarction as well as the development of specialized “stroke centers” in an attempt to improve outcome in patients with cerebral ischemic infarction. These interventions have improved the outcomes in acute ischemic infarction; however, the 30-day mortality following acute stroke is still unacceptably high at 15% to 30%.⁴ The recent positive outcome of multiple endovascular trials introduces a new paradigm for treatment of ischemic stroke with proximal vessel occlusion and a significant penumbra. The door has opened for the determination of best practice combining systemic lytic and intra-arterial therapies.

It is now even more important for the emergency physician to be able to recognize acute ischemic infarction, order appropriate imaging studies, initiate intravenous (IV) thrombolytic therapy and rapidly consult neurologists and interventional specialists. This paradigm is akin to the treatment of ST-elevation myocardial infarction (STEMI). This chapter will review (1) basic neurologic syndromes as localized by their arterial distributions (i.e., anterior cerebral artery [ACA], middle cerebral artery [MCA], posterior cerebral artery [PCA], basilar artery, etc.) as an effort to simplify recognition of large-vessel infarctions, (2) new imaging modalities, (3) initial medical management, and (4) interventional management.

RECOGNIZING ACUTE ISCHEMIC INFARCTION

Because computed tomography (CT) scans do not “rule out” acute ischemic infarctions, the non-neurologist must perform a detailed neurologic examination. Identifying these patterns can assist in the identification of stroke syndromes that can be treated with thrombolytic therapy, as opposed to stroke syndromes that do not follow vascular territories such as hemorrhages; venous infarctions (extremely rare); or stroke mimics such as extreme ranges of blood sugar, seizures, or tumors. The history of a sudden onset of neurologic deficit and the time of onset are paramount to making diagnosis and treatment decisions.

The presentation of acute stroke follows distinctive anatomic patterns that are predictive of the involved arterial

territory. Here are the anatomic structures and associated syndromes as supplied by each major vessel:

- **ACA:** The first segment (A1) of the ACA gives rise to the recurrent artery of Huebner that supplies the caudate head, anterior limb of the internal capsule, and anterior aspect of the putamen and globus pallidus (there is some variability). Infarcts to these structures can result in confusion and arm and face weakness. The remainder of the ACA supplies the medial surface of the cerebral hemisphere and the superior aspect of the frontal and parietal lobes. Infarcts in these territories may result in lack of initiative, abulia, paratonia (“gegenhalten”; anterior frontal lobes), contralateral leg paralysis (superior aspect of the motor cortex—the precentral gyrus), and, to a lesser extent, arm paralysis (in particular, the shoulder). In bilateral frontal infarction, akinetic mutism, paraplegia, incontinence, and apathy with amnesia may result. Lower extremity contralateral sensory loss may be present if the postcentral gyrus is affected. Other nuances may occur in ACA territory strokes, but these are out of the scope of this review.
- **MCA:** The MCA is the most common site of ischemic stroke and the largest branch of the internal carotid artery (ICA). It supplies the majority of the lateral surface of the cerebral hemisphere and the deep structures of the frontal, insular, and parietal lobes. The lenticulostriate arteries arise off the M1 segment and supply the corona radiata, external capsule, claustrum, putamen, part of the globus pallidus, body of the caudate nucleus, and superior aspect of the anterior and posterior limbs of the internal capsule. The clinical picture of the MCA territory infarction depends on the site of occlusion. Contralateral face, arm, and leg weakness manifests when the precentral gyrus (primary motor cortex) is affected. Contralateral face, arm, and leg sensory loss occurs when the postcentral gyrus (primary sensory cortex) is affected. Gaze preference to the affected side may occur when the frontal eye fields are affected. In the dominant hemisphere, the various aphasia occur when Wernicke’s, Broca’s, or communicating fibers are affected. Complicated sensory syndromes such as alexia with agraphia (left angular gyrus) and combinations of finger agnosia, acalculia, right–left disorientation, and agraphia (Gerstmann syndrome) may also be encountered in posterior MCA territory infarctions. Neglect, denial (anosognosia), apraxias, sudden confusional states, and agitated delirium may also occur with parietal lobe infarctions. Contralateral visual field cuts (homonymous hemianopsia, or homonymous inferior quadrantanopsia) may occur if the parietal radiations are affected. Clinical manifestations of infarcts to the lenticulostriate territory include hemiplegia and, less often, dysarthria alone or upper limb clumsiness. Of course, other nuances to MCA territory ischemic infarctions exist that are out of the scope of this review.
- **PCA:** The PCA is the terminal branch of the basilar artery; however, 25% of the time it has an embryonic

origin off the ICA (aka fetal PCA). The PCA supplies the occipital lobes and the inferomedial portions of the temporal lobes. Numerous small branches off the P1 segments and sometimes the top of the basilar artery supply the mesencephalon, thalamus, and adjacent structures. Proximal PCA occlusion may simulate MCA occlusion when it causes hemiparesis, hemianopsia, hemispatial neglect aphasia, and sensory loss. Cortical signs may be pseudolocalizers in the event of thalamic involvement. The PCA gives a splenial branch (splenium of the corpus callosum) that forms an anastomosis with the ACA. Infarction of the splenium can result in alexia without agraphia, “pure word blindness,” and sometimes color anomia and/or object/photograph anomia. The cortical branches of the PCA are the anterior temporal, posterior temporal, parieto-occipital, and calcarine arteries. These supply the inferior aspect of the temporal lobe and the parietal radiations and terminate with the calcarine branch that supplies the visual cortex. Cortical PCA branch occlusion almost always presents with a contralateral visual field cut. Involvement of the



TABLE 33-1: Posterior Circulation Syndromes

1. Ipsilateral oculomotor palsy with contralateral cerebellar ataxia (Nothnagel syndrome)
2. Ipsilateral oculomotor palsy with contralateral hemiplegia (Weber syndrome)
3. Ipsilateral oculomotor palsy with contralateral ataxia and hemichoreoathetosis (Benedikt syndrome)
4. Nuclear oculomotor palsy (rare), characterized by:
 - a. Unilateral oculomotor weakness with contralateral superior rectus weakness
 - b. Bilateral oculomotor weakness with sparing of the levator palpebra
5. Unilateral internuclear ophthalmoplegia (INO): inability of the affected eye to cross the midline medially
6. Wall-eyed bilateral internuclear ophthalmoplegia (WEBINO syndrome): neither eye can cross the midline medially
7. Dorsal rostral midbrain (Parinaud syndrome) characterized by:
 - a. Supranuclear upward gaze palsy
 - b. Defect of convergence
 - c. Convergence-retraction nystagmus
 - d. Light-near dissociation
 - e. Collier’s sign (lid retraction)
 - f. Skewed deviation
8. Pseudoabducens palsy: no lateral eye movement on the affected side
9. Midbrain corectopia
10. Peduncular hallucinosis, primarily visual lesions of mobile objects, often animated, colorful, and frequently pleasant: no hallucinations occur with mid and cephalic lesions involving the cerebral peduncles or the medial substantia nigra pars reticulata bilaterally
11. Decerebrate rigidity
12. Locked-in syndrome
13. Disturbances of consciousness

calcarine artery may be associated with ipsilateral eye pain. Involvement of bilateral PCAs may result in cortical blindness. Patients are often unaware of their “cortical blindness” (Anton’s syndrome).

- Vertebral and basilar arteries: The vertebral arteries give rise to the posterior inferior cerebellar arteries (PICAs) that supply the inferior cerebellum and inferior vermis. Infarcts here result in ataxia. The vertebral arteries then merge in what is referred to as the vertebral–basilar junction (VBJ) to give rise to the basilar artery. The basilar artery gives rise to the anterior inferior cerebellar arteries (AICAs), which when infarcted result in ataxia and possible hearing loss if the labyrinthine artery arises off the AICA. The superior cerebellar artery (SCA) is near the top of the basilar artery and supplies the superior vermis and the superior aspect of the cerebellar hemispheres. Infarcts here can vary from limb ataxia to truncal ataxia or both. The mid and the top segments of the basilar artery give off perforating branches into the brainstem (medulla and pons) and thalamus/midbrain, respectively. The top of the basilar branches has overlap with the perforating branches that arise off the P1 segments of the PCAs. These perforating vessels allow for the plethora of “posterior circulation syndromes” (Table 33-1).

IMAGING IN ACUTE STROKE

Differentiating an acute ischemic stroke from an intracranial hemorrhage is impossible by history and physical exam alone. Thus, a CT must be done to rule out hemorrhage in order to

move forward in the time-sensitive evaluation for the administration of rt-PA. It is important to note that acute ischemic stroke is usually not visible on a CT scan in its early stages (typically < 6 hours), but in some cases increased attenuation of the proximal MCA may be seen. This “hyperdense MCA sign” is associated with thrombus.

Imaging has progressed in several fronts. Magnetic resonance imaging (MRI) has the diffusion-weighted imaging (DWI) sequence where acute ischemic stroke can be seen within minutes of infarction. CT scanning remains more commonly available in the emergency department and has the advantage of being quickly and easily obtained. To this end, progress in CT scanning includes CT angiography (CTA) and CT perfusion (CTP). MRI advances also include the perfusion sequences.

With CTA, it is now possible to identify large-vessel occlusions in the brain within seconds. In addition, part of the etiologic workup of the stroke can be attained simultaneously by performing a CTA of the neck. Carotid stenosis and intracranial vessel integrity (occlusion, vasculopathy, dissection, or stenosis) can be determined within minutes of performing the initial head CT.

Perfusion studies have been referred to as “physiologic imaging.” In simple terms, perfusion imaging can determine a delay in the arrival of contrast (blood) to the vascular bed in question. If there is a delay to a certain territory, say the right MCA, for example, one can spend more time analyzing the vasculature leading to and including the right MCA in the hopes of identifying (1) a treatable source (e.g., carotid stenosis) and (2) the actual clot/occlusion causing the stroke (Figure 33-1).

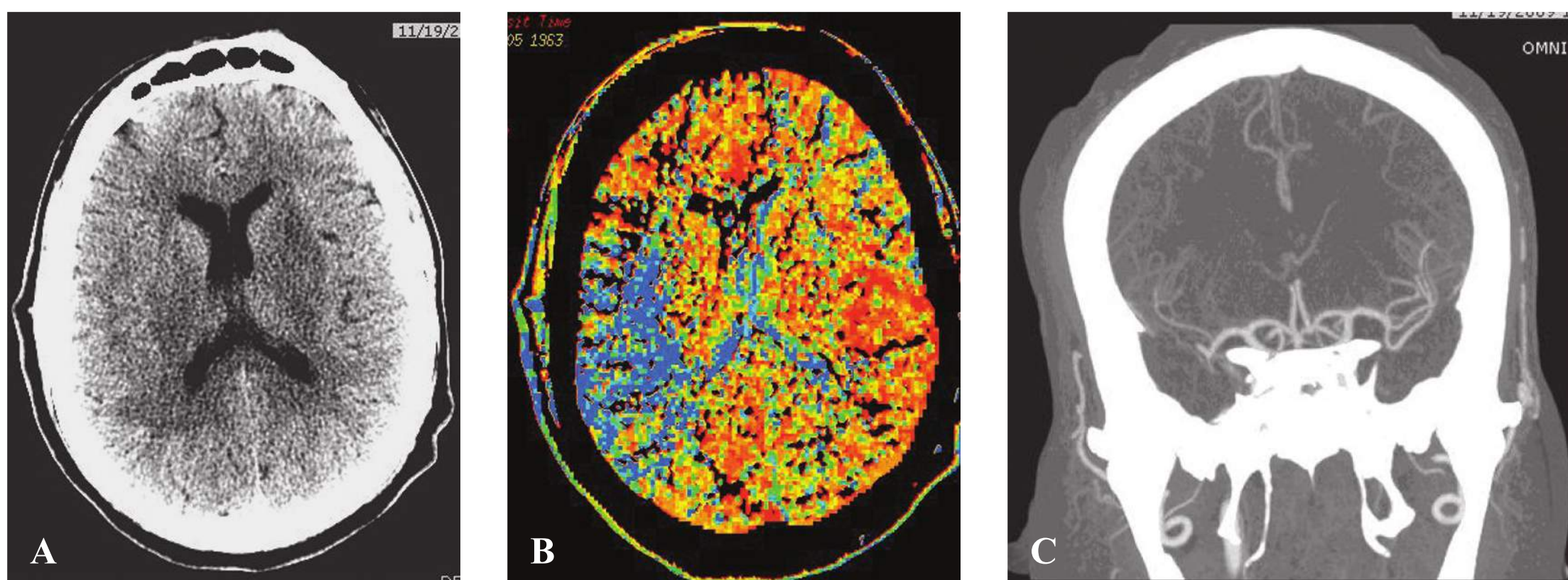
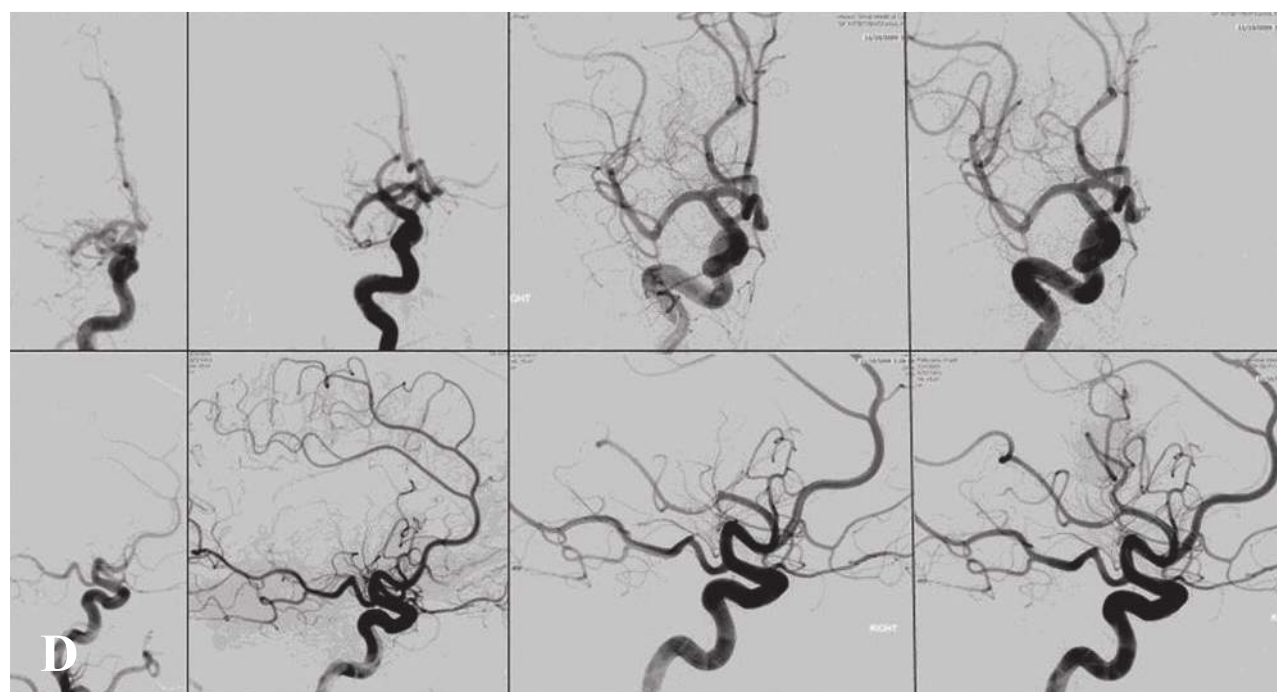


FIGURE 33-1 (A–D) A 46-year-old man presented with left face, arm, and leg hemiplegia (NIHSS 20). CT demonstrates no hemorrhage. CT perfusion demonstrates elevated mean transit time (MTT) in the right MCA territory. CTA demonstrates occlusion of the right distal M1/proximal M2 segment. Angiography confirms the occlusion despite intravenous rt-PA. The occlusion was recanalized successfully with 11 mg intra-arterial rt-PA and wire disruption of the clot. Postprocedure, the patient’s residual deficit was mild nasolabial flattening.



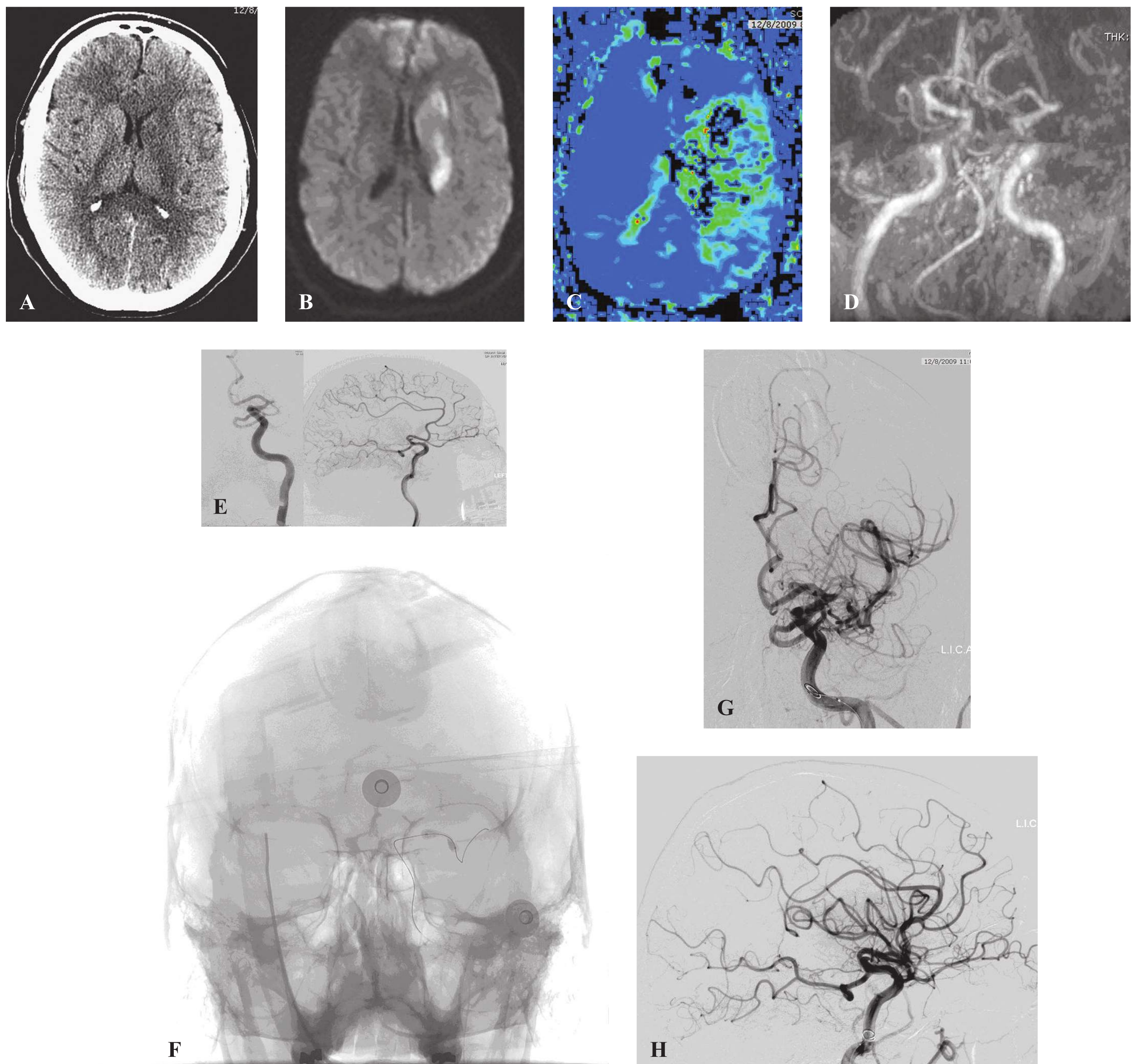


FIGURE 33-2 (A–H) A 45-year-old man presents with sudden onset of global aphasia and 2/5 hemiparesis at 3.5 hours onset time. The patient was not given IV rt-PA, although now, in light of ECASS III, he would have been a candidate. CT demonstrates no hemorrhage. Early findings in the caudate are more obvious on MRI/DWI. MRI perfusion demonstrates a full MCA territory perfusion defect. This case demonstrates well the concept of diffusion–perfusion mismatch. Clearly, there is brain to save (penumbra). The MRA demonstrates an occlusion of the left MCA M1 segment. Angiography confirms the left M1 occlusion. Intra-arterial rt-PA and the MERCI device were used unsuccessfully in efforts to recanalize the vessel. Angioplasty was performed successfully, leaving a mild residual stenosis. This correlates to the pathophysiology because the patient was using cocaine the previous night. Recall that cocaine induces transient platelet aggregability, vasospasm, and cardiac arrhythmias secondary to sympathomimetic effects. The patient’s residual deficit correlates to the original MRI/DWI: deficits that localize to the caudate. This is a clear demonstration of perfusion defect correlating to reversible deficits—proof of concept of the penumbra saved.

Physiologic imaging has further progressed with analysis of the concept of “mismatch.” Infarcted or otherwise dead tissue can be demonstrated on MRI DWI. Perfusion defects may be equal to the amount of tissue already dead, or they can be greater, giving rise to a new definition of penumbra:

underperfused territory that is at risk of dying and therefore amenable to treatment (Figures 33-2 and 33-3).

Some centers include multimodal CT/MRI options in the decision making for acute stroke patients. This combination of imaging can provide information about the nature of

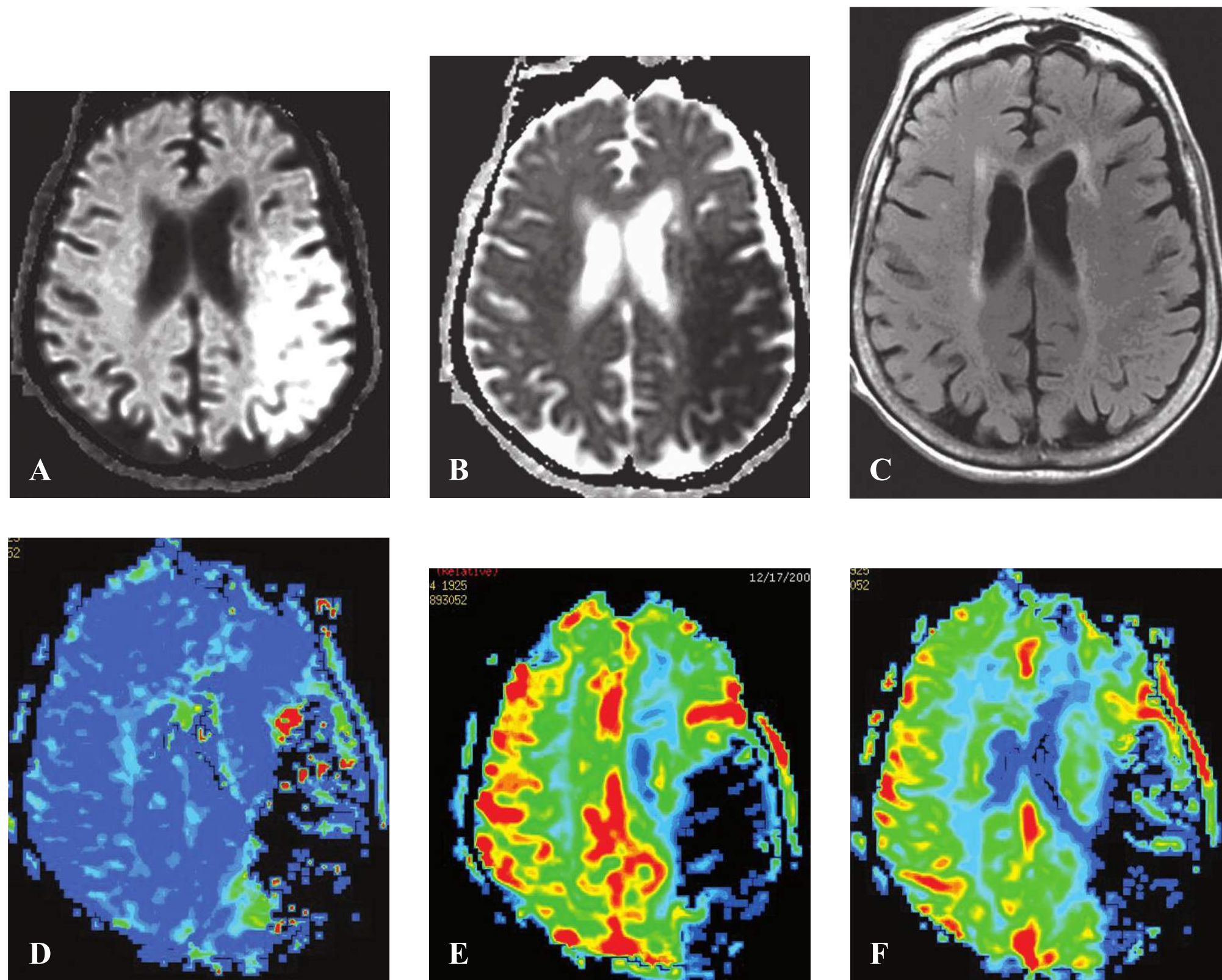


FIGURE 33-3 (A–F) Matched diffusion–perfusion defect. This patient is not a candidate for interventional or arguably intravenous thrombolysis because the area of infarction (hyperintense on DWI) matches the area of perfusion defect, making this a “completed infarction” in this 84-year-old woman with sudden-onset aphasia, right hemiplegia, right hemisensory loss, and right homonymous hemianopsia in the context of atrial fibrillation.

the stroke, as well as the acute process of ischemia, including reversibility, to help risk-stratify the patient for systemic or interventional treatment.⁵

MEDICAL MANAGEMENT OF ACUTE ISCHEMIC STROKE

The NINDS trial in 1995 provided evidence that intervention is possible in the setting of ischemic stroke. By administering IV rt-PA within 3 hours, 30% of patients improved to near-normal exams at 3 months with a 6% risk of intracranial hemorrhage (ICH). However, only a small percentage of patients are candidates for IV rt-PA. Even in the subgroup receiving thrombolytic therapy, appropriate supportive care can significantly reduce morbidity.

The ABC’s

Although the majority of patients with acute ischemic stroke will not require intubation or ventilatory support, endotracheal intubation should be considered in those patients who are obtunded or those who have lost airway protective reflexes. Also, many patients will have impaired mobility of their oropharynx, placing them at risk for aspiration. Because pneumonia has been shown to be an important cause of death after

cerebrovascular events,⁶ it is prudent to keep these patients NPO until their swallowing ability has been evaluated.

Blood pressure (BP) management immediately following acute ischemic stroke remains somewhat controversial. Hypertension is common in the immediate poststroke period and is felt to be a protective response—an attempt to provide adequate perfusion to the ischemic penumbra that surrounds the area of acute infarct. There is some evidence demonstrating a correlation between hypertension in the first 24 hours after stroke and increased mortality.^{7,8} There is also evidence that rapid reduction of BP may contribute to morbidity after acute stroke.⁹ It is generally believed that extreme hypertension contributes to poor outcome in the setting of stroke, but there is no evidence that clearly defines the upper limits of BP that should be considered a trigger for therapy. This is not the case in those patients receiving thrombolytic therapy, where there are clearly defined limits (systolic BP [SBP] < 185 mm Hg and diastolic BP [DBP] < 110 mm Hg) beyond which the risk of ICH is increased.¹⁰

The current American Heart Association/American Stroke Association (AHA/ASA) guidelines for management of hypertension in acute stroke are as follows:

- Aggressive management of BP should be considered in all patients who demonstrate evidence of severe end-organ damage from hypertension in addition to

acute stroke. This includes patients with hypertensive encephalopathy, acute renal failure, aortic dissection, acute myocardial infarction (MI), or acute congestive heart failure.

- If a patient will be undergoing thrombolytic therapy or other reperfusion intervention, BP should be lowered to an SBP of < 185 mm Hg and a DBP of < 110 mm Hg.
- In those who are not candidates for intervention, a less aggressive approach is recommended. Antihypertensive agents should be held until SBP remains above 220 mm Hg or DBP remains above 120 mm Hg.

In all instances, it is recommended that the agent of choice be easily titratable to prevent rapid sustained declines in BP. The current guidelines recommend labetalol 10 mg IV repeated every 10–20 minutes to a maximum dose of 200 mg, labetalol 10 mg IV followed by a 2–8 mg/min infusion, or nicardipine infusion starting at 5 mg/h and titrated to desired BP or a maximum dose of 15 mg/h.¹¹ Hypotension is uncommon in patients with acute stroke. If it develops, the cause should be actively sought—aortic dissection, acute MI, and the like. Cardiac dysrhythmias, blood loss, or volume depletion should all be considered. Therapy should be directed at the underlying cause and may include volume replacement and pressors if hypotension persists. Certainly patients may sustain ischemic infarction in the setting of arterial stenosis and hypotension. Neurovascular imaging is warranted (CTA or MRA of the head and neck).

Management of Glucose

Hyperglycemia is a common phenomenon immediately post-stroke and has been shown to be associated with worsened outcome. The correlation is strongest in the population without diabetes mellitus. Hyperglycemia in the critically ill is often referred to as stress hyperglycemia and is characterized by elevation in catecholamines, cortisol, growth hormone, glucagon, gluconeogenesis, insulin levels, insulin resistance, and insulin-like growth factor-1 (IGF-1) protein. There is evidence that hyperglycemia worsens outcome and increases the risk of ICH in patients receiving rt-PA.¹² Although current evidence demonstrates worsened outcome in the setting of hyperglycemia poststroke, there is no solid evidence to guide the means of therapy or the level to which glucose control should be maintained. The majority of randomized controlled trials (RCTs) available that deal with glucose control are studies that looked at insulin therapy in patients in the intensive care unit (ICU) setting for illnesses other than stroke. These studies indicate variable benefit from tight glycemic control and demonstrated a significant risk of hypoglycemia with worsened outcome in patients in the treatment arm.¹³ The largest RCT looking specifically at tight glucose control in stroke patients is the GIST-UK trial. The methods for maintaining infusion and monitoring glucose were highly labor intensive, and the results were neutral with effect on morbidity and mortality.¹⁴ The current AHA/ASA guidelines are to begin intervention for serum glucose levels of > 140–185 mg/dL and to try to maintain levels between

80 and 140 mg/dL. Therapy can involve repeated boluses of insulin or IV infusion.¹¹ In all instances, careful monitoring is needed, and hypoglycemia should be avoided as this also has been shown to have a negative effect on patient outcome.

THROMBOLYSIS IN ACUTE STROKE

The goal of the treatment of acute ischemia is rapid reperfusion in patients who present within the therapeutic window. Every ischemic stroke patient must be evaluated quickly. Time is brain. Early stroke treatment is associated with better outcome.¹⁵ Treatment of the symptoms of ischemic infarction begins as soon as the diagnosis is made; in other words, once the CT scan excludes the hemorrhage. Give aspirin. Aspirin has been shown in numerous trials to reduce the frequency of subsequent ischemic events.¹⁶ Per rectum aspirin may be safely administered in patients with swallowing or face weakness.

With the publication of the NINDS trial in 1995, thrombolytic therapy entered the spotlight. The study demonstrated significant benefit of therapy, but also demonstrated a 6% risk of ICH in the treatment arm. Significant controversy ensued among the emergency medicine community. Did the benefit of lytics outweigh the risk? Could rt-PA be safely used in the community setting? Can thrombolytic therapy safely be initiated in the absence of a neurologist? A plethora of research ensued.

As of 2015, thrombolytic therapy is widely accepted and is widely used throughout the United States and Europe. However, not all hospitals have initiated protocols for the use of rt-PA in this setting. This may be due to a lack of neurology coverage in many areas of the country—it is estimated that 20% of the population is served by emergency departments that lack immediate access to a neurologist. The literature supports the use of thrombolytics even in the absence of an onsite neurologist. Teleneurology is becoming increasingly popular and has been shown to be safe and efficacious.^{17,18} Also, in spite of subtleties in stroke presentation, accuracy of diagnosis by emergency physicians has been demonstrated,¹⁹ and thrombolytic treatment can be safely initiated using a standard protocol even in the absence of a neurologist.²⁰ Current evidence-based medicine indicates that rt-PA can be safely used in the community setting as long as strict adherence to protocols is maintained. The rate of ICH remains at 6% in most studies, but has been noted to be lower (1.7%) in the SITS-MOST observational study.²¹ The current AHA/ASA guidelines¹¹ for the use of rt-PA in the setting of acute ischemic stroke recommend treatment for patients who fit the following profile: Patients must have a measurable neurologic deficit that is not clearing spontaneously and is not minor and isolated. In those with more severe deficits—National Institutes of Health Stroke Scale (NIHSS) > 22—caution is advised because although there may be some benefit to therapy, there is a significant increase in the incidence of ICH. Contraindications to rt-PA therapy are listed in Table 33-2.

Older age is not in and of itself a contraindication to thrombolytic therapy. Prior suggestions that rt-PA should be withheld in patients older than 80 years have been



TABLE 33-2: Contraindications to Recombinant Tissue Plasminogen Activator (rt-PA) Therapy

1. Head trauma in the preceding 3 months
2. Myocardial infarction in the preceding 3 months
3. GI or urinary tract hemorrhage in the preceding 21 days
4. Major surgery in the preceding 14 days
5. Any history of prior intracranial hemorrhage
6. Arterial puncture at a noncompressible site in the past 7 days
7. Active bleeding or acute trauma/fracture on current physical examination
8. Elevated aPTT or INR > 1.7
9. Platelet count below 100,000/mm³
10. Hypoglycemia (< 50 mg/dL)
11. Seizure with postictal neurologic deficits
12. CT with multilobar infarction (> 1/3 the cerebral hemisphere)
13. Hypertension (SBP > 185 mm Hg and/or DBP > 110 mm Hg)

questioned, and data analysis has shown that there is some benefit to treatment in this age group. Overall, these patients still have poorer outcomes than younger patients when suffering an acute stroke, but the incidence of ICH among this population is not higher than in younger patients treated with thrombolytics.^{22,23}

The recommended dose of rt-PA in the setting of acute stroke is 0.9 mg/kg with a maximum dose of 90 mg. The initial 10% of the dose is administered as an IV bolus given over 1 minute, and the remaining is infused over 60 minutes. It is markedly important to obtain a weight on all patients in whom thrombolysis is considered. Overestimation of weight and subsequent overdosing of rt-PA is one of the more common violations of protocol and is thought to contribute significantly to the incidence of ICH in this patient population.²⁴ Another frequently noted protocol violation is failure to adequately control BP. Frequent monitoring of BP should be initiated in these patients, and antihypertensives should be administered if the SBP is ≥ 180 mm Hg and the DBP is ≥ 105 mm Hg.

The decision to treat patients with thrombolytics is time dependent. In the initial NINDS trial, there was a significant increase in the incidence of ICH in patients receiving rt-PA > 3 hours after symptom onset. For years, the “3-hour window” has been the gold standard. Over the past 5 years, multiple studies have asked the following question: Is it possibly safe to expand this therapeutic window? The most definitive is the European Cooperative Acute Stroke Study (ECASS) III trial, published in September 2008. The trial was multicentered, randomized, and placebo-controlled and enrolled patients with stroke onset 3–4.5 hours prior to receiving therapy. There was a significant improvement in neurologic outcome at 90 days in the treatment group. The incidence of ICH was also larger in the treatment arm, with symptomatic ICH occurring in 2.7% of those receiving lytics. There was no significant difference in mortality between the groups.²⁵ As a result of this trial, the AHA/ASA guidelines for the use of thrombolytics in acute stroke have been revised. It is now a

Class IB recommendation for lytics to be used in patients for up to 4.5 hours after the onset of symptoms.²⁶ Since the publication of the 2009 guidelines, administration of IV rt-PA and IA rt-PA has increased for both the 0–3 as well as the 3–4.5 hour windows, along with a documented decrease in overall spontaneous ICH.²⁷

Even so, there will be patients who are not candidates for IV thrombolysis or those who present with a greater delay after symptom onset. These patients need no longer all fall into the category of “supportive care only.” Over the past 15 years, an entire specialty, interventional neuroradiology, has developed, and a multitude of techniques have been added to the therapeutic armamentarium.

INTERVENTIONAL MANAGEMENT OF STROKE

Interventional therapies for acute ischemic infarction have been the hope of neurologists and neurointerventionalists since the early 2000s. This modality has not been supported by positive outcome data until 2015, with the publication of four randomized trials showing positive outcomes for patients receiving endovascular therapy along with systemic rt-PA for acute ischemic stroke with large-vessel anterior occlusions. The success of these trials was in contradistinction to several previous trials, which used older technology. The combination of new technology, the stent-retriever, and imaging-based selection of patients that focused on those with a small ischemic core and significant penumbra amenable to improvement with reperfusion were the most likely reasons for success in these studies. This opened up a new paradigm in the treatment of acute ischemic stroke and will likely lead to changes in regional stroke systems.^{28–31}

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Intracerebral Hemorrhage

Katherine A. Pollard • Timothy J. Ellender

□ SPONTANEOUS INTRACEREBRAL
HEMORRHAGE 349

□ SUBARACHNOID HEMORRHAGE 353

SPONTANEOUS INTRACEREBRAL HEMORRHAGE

Intracerebral hemorrhage (ICH) accounts for more than 10% of all strokes with approximately 79,000 cases in the United States per year.¹ These patients have a high mortality (> 25%), and survivors often have profound neurologic deficits, with only the minority of patients regaining functional independence at 6 months.^{2,3}

The incidence of ICH increases exponentially with age and is higher in men than in women. Independent risk factors for ICH include hypertension (the most significant risk factor, present in > 75%), alcohol abuse, thrombolytic therapy, cocaine or amphetamine use, cigarette smoking, and diabetes mellitus.^{4,5}

Anticoagulant therapy and daily aspirin use are also independent risk factors for ICH. In a meta-analysis of the literature, for every 1,000 patients treated with aspirin for 5 years, there will be one excess ICH caused by this therapeutic intervention. On the other hand, 14 acute myocardial infarctions will be avoided in this same population, so benefits of therapy far outweigh risk.⁶ Patients on anticoagulant therapy have a 7- to 10-fold higher incidence of ICH.⁷ The mortality in this population is approximately 60%—almost double that of the general population.^{8,9} ICH occurs in 2–9 per 100,000 patients receiving anticoagulant therapy per year.¹⁰ A strong association between over-anticoagulation and ICH exists; however, the majority of bleeds occur in patients with a therapeutic international normalized ratio (INR).^{8,9}

This chapter will discuss the diagnosis and management of spontaneous ICH and will then separately address diagnostic and management strategies for subarachnoid hemorrhage (SAH).

Presentation and Diagnosis

Patients with an ICH generally present with sudden onset of neurologic deficits (Figure 34-1). These are often rapidly progressive. A full neurologic examination including mental status, cranial nerves, motor strength, sensory, reflexes, and cerebellar coordination should be documented on presentation to the emergency room and followed sequentially (hourly neuro checks). Exam findings can help localize the lesion, but more importantly, form the baseline to evaluate for signs of deterioration. Cerebral hemispheric subcortical white matter or putamenal hemorrhages can present with gaze deviation (involvement of eye fields—gaze toward the lesion) and/or contralateral hemiparesis/plegia, aphasia (dominant side—perisylvian subcortical white matter), neglect or agnosias (parietal subcortical white matter), and contralateral hemianopsia (occipital lobe subcortical white matter). Thalamic hemorrhages can present with aphasia (dominant side), neglect (nondominant side), contralateral sensory or motor deficits (if adjacent internal capsule motor fibers are involved), oculomotor derangements, visual field cuts, and/or small reactive pupils. Brainstem lesions can present with coma, quadriplegia, locked-in syndrome, horizontal gaze paresis, ocular bobbing, pinpoint pupils, nystagmus, hyperthermia, and abnormal breathing patterns. Fixed midposition pupils and hippus are suggestive of midbrain involvement. Cerebellar hemorrhages can present with limb or truncal ataxia, nystagmus, skewed gaze, brainstem findings secondary to mass effect on the brainstem, and signs of elevated intracranial pressure (ICP)/hydrocephalus from complete effacement of the fourth ventricle or cerebral aqueduct.

The diagnostic test of choice at this time remains noncontrast computed tomography (CT). CT angiography (CTA) is useful in identifying aneurysms or vascular malformations.

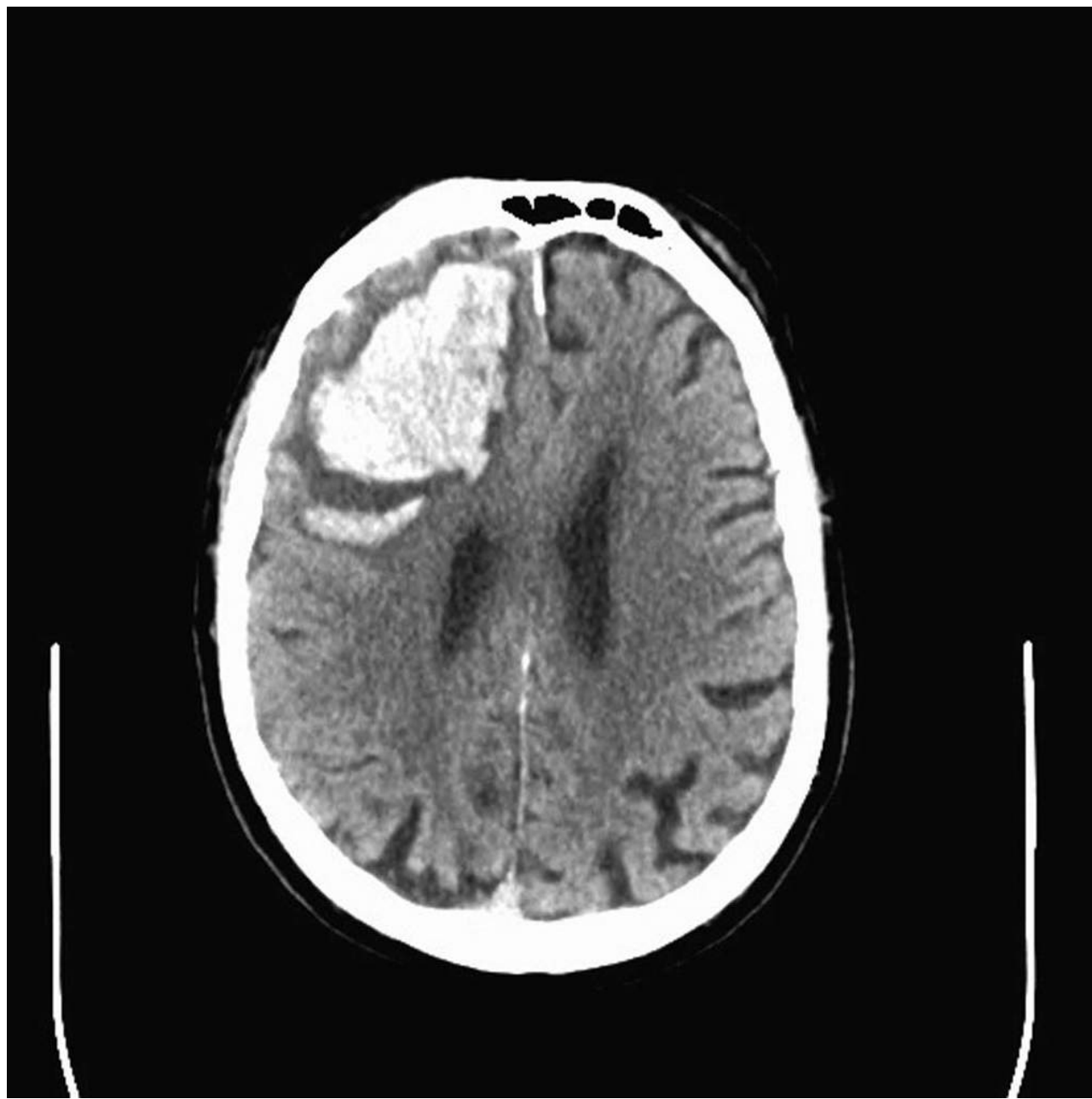


FIGURE 34-1 CT lobar hemorrhage. The patient presented with sudden-onset left-sided weakness with alteration of consciousness.

Active bleeding can be seen as contrast extravasation into the hematoma “spot sign” on these studies (Figure 34-2). Increase in ICH is seen in 26% of patients within the first hour of hospital presentation.¹¹ Hemorrhages from chronic hypertension commonly occur in the basal ganglia, thalamus, pons, and



FIGURE 34-2 CTA frontal intracerebral hemorrhage with “spot sign.” The patient presented with sudden-onset headache, nausea with vomiting, altered mentation, and left sided deficits (left hemiparesis, left facial droop, and left-sided neglect). Coronal sequence is particularly useful at demonstrating uncal herniation.

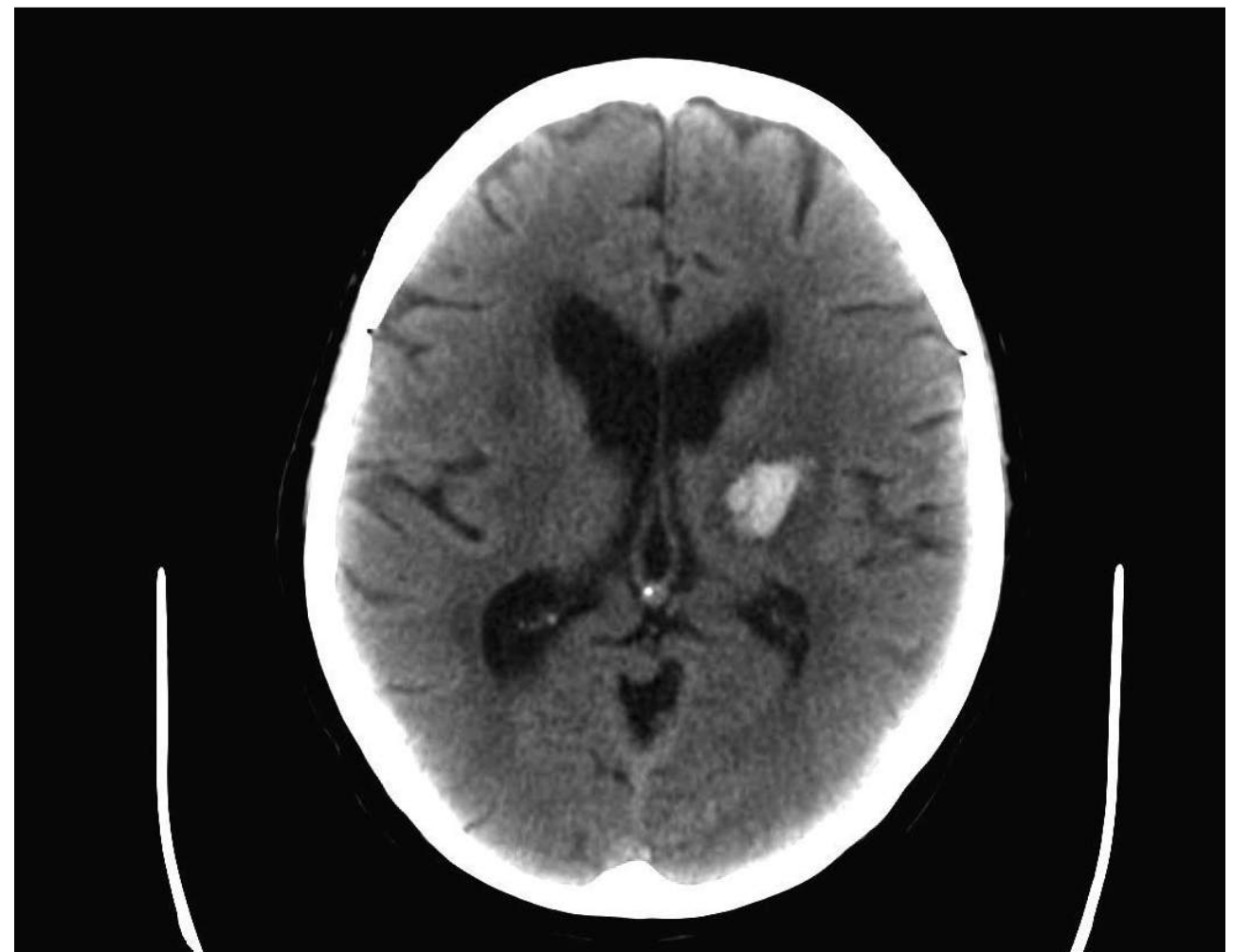


FIGURE 34-3 CT hypertensive hemorrhage. Note the left thalamic hemorrhage; this most commonly results from damage to the penetrating branches of the posterior cerebral artery. The site of hypertensive hemorrhages is most commonly in the territory of perforating vessels (basal ganglia—lenticular striate arteries; pons—basilar perforators; thalamus—thalamoperforators).

cerebellum, among other sites (Figure 34-3). These sites are supplied by perforating vessels that are susceptible to lipohyalinosis, fibrinoid necrosis, and Charcot–Bouchard microaneurysms in the setting of chronic hypertension. Hemorrhages from amyloid angiopathy usually occur in a lobar distribution. This disease, characterized by β -amyloid deposition in small- and medium-sized vessels, can occur spontaneously or in association with Alzheimer’s disease, recurrent hemorrhages (of various sorts—subdural, subarachnoid, etc.), or hereditary syndromes associated with the Apo E2 and E4 alleles. Hemorrhages from vasculopathy usually result from rupture of small- or medium-sized vessels. History is critical in making this diagnosis because typically the hemorrhage is preceded by months of headache and neurologic deficits such as cognitive decline and psychiatric symptoms from multiple small strokes. Vasculopathy can be seen with infectious diseases such as herpes, tuberculosis, bacterial/fungal/viral vasculitis, syphilis, systemic diseases such as polyarteritis nodosa, Wegener’s granulomatosis, Churg–Strauss syndrome, systemic lupus erythematosus, rheumatoid arthritis, Sjögren’s disease, hepatitis, Behçet’s disease, sarcoidosis, drug induced (cocaine), and more.

Medical Management of Patients with ICH

AIRWAY MANAGEMENT

Patients with ICH often deteriorate rapidly and require careful monitoring of their airway. Endotracheal intubation should be performed in patients with Glasgow Coma Scale (GCS) score of 8 or lower or those unable to manage secretions. If patients require transfer from a carefully monitored

setting or to an outside facility, realize that there is the potential for these patients to suffer airway compromise, and consider intubation in patients who are obtunded. At least 20% of patients will experience a decrease in their GCS of ≥ 2 points between the prehospital emergency medical services assessment and the initial evaluation in the emergency department (ED).¹²

Rapid sequence induction should be performed prior to intubation. The use of lidocaine prior to intubation has not been proved to prevent increases in ICP and is of questionable benefit.¹³ The preferred induction agents should be short acting and should not increase ICP. Current recommendations are for the use of etomidate or propofol in the setting of acute ICH. Propofol can cause a rapid decrease in blood pressure (BP), but this generally is responsive to boluses of isotonic fluids. Midazolam should be avoided as it may adversely affect ICP.¹⁴ A short-acting nondepolarizing agent such as rocuronium is preferred to the shorter-acting succinylcholine in patients at risk for increased ICP. The evidence is incomplete, but it does suggest that succinylcholine may increase ICP in those with a space-occupying lesion in the cranium.^{15,16} If a decision is made to use succinylcholine, pretreatment with a “defasciculating” dose of a nondepolarizing agent such as vecuronium or pancuronium should be employed because this has been demonstrated to protect against such increases in ICP.^{15,16}

There are no unique aspects to ventilator management in patients following acute ICH. Hyperoxygenation is not necessary, and hyperventilation should be reserved as a temporizing measure for patients with elevations in ICP. Positive end-expiratory pressure (PEEP) of up to 12 mm Hg may safely be used and will not increase ICP so long as mean arterial pressure (MAP) is maintained.¹⁷

BLOOD PRESSURE MANAGEMENT

There is still some controversy over definite limits at which to begin therapy for hypertension in patients following spontaneous ICH. Prior literature showed possible increases in morbidity and mortality accompanying aggressive management of hypertension. However, two recent trials, the INTERACT and the ATACH trials, demonstrated that it is safe to aggressively lower BP in patients with ICH.^{18,19} These studies are not sufficient to establish parameters for BP control, nor do they provide sufficient evidence to demonstrate improved outcome in patients receiving aggressive early lowering of BP. Subsequent trials INTERACT II and ATACH-II are further exploring these issues.^{20,21} As such, the American Heart Association/American Stroke Association (AHA/ASA) continues to support the 2010 recommendations²² as follows:

- If systolic BP (SBP) is > 200 mm Hg or MAP is > 150 mm Hg, consider aggressively lowering pressure using an agent given by intravenous (IV) infusion.
- For SBP > 180 mm Hg or MAP > 130 mm Hg in the setting of possible increased ICP, consider lowering BP via either continuous infusion or intermittent administration of IV medications while monitoring the ICP

and maintaining a cerebral perfusion pressure of (CPP) ≥ 60 mm Hg.

- Consider lowering BP to 160/90 mm Hg or MAP of 100 mm Hg if SBP > 180 mm Hg or MAP is > 130 mm Hg in patients with no evidence of increased ICP. Again, continuous IV infusion or intermittent dosing of medication is appropriate.

The guidelines also including the following: If a patient presents with an SBP of 150–220 mm Hg, it is probably safe to acutely lower the SBP to 140 mm Hg.

In general, agents chosen for BP control in this setting should be easy to titrate and have a relatively short duration of action. The most frequently recommended agents include IV nicardipine, labetalol, or esmolol.

MINIMIZING HEMATOMA EXPANSION

It is widely recognized that hematoma expansion during the first 6 hours after an ICH is predictive of poor outcome.²³ Patients with coagulopathy, be it inherent or iatrogenic, should receive agents that attempt to correct the abnormality and therefore limit hematoma size. Patients who have a severe coagulation factor deficiency or severe thrombocytopenia should receive appropriate factor replacement or platelets.²²

In patients who have received recombinant tissue plasminogen activator (rt-PA) and suffer symptomatic ICH, there are no solid guidelines available. Current recommendations are to infuse cryoprecipitate that contains factor VIII.²⁴

In patients suffering ICH who have been on heparin, reversal with protamine sulfate, 1 mg for every 100 U of heparin given (within the first 30 minutes of heparin administration), is indicated; 0.5 to 0.75 mg/100 U heparin of protamine within 31–60 minutes, 0.375 to 0.5 mg/100 U heparin of protamine within 61–120 minutes, and 0.25 to 0.325 mg/100 U heparin of protamine at > 2 hours of heparin administration, keeping in mind the half-life of heparin is 2 hours. The total dose should not exceed 50 mg, and protamine should be injected slowly by IV because rapid infusion may trigger hypotension.²⁵

People receiving oral anticoagulants, such as warfarin, account for 12–14% of all ICH patients.²⁶ The current AHA/ASA guidelines for patients with elevated INR are to (1) withhold warfarin, (2) give IV vitamin K (dose: 2 mg, slow IV)—be prepared for a possible anaphylactic response when administering IV vitamin K, and (3) use either fresh frozen plasma (FFP) 15 mL/kg or prothrombin complex concentrates (PCC) 50–150 mL to provide vitamin K-dependent clotting factors. PCC may hold some benefit over FFP as there is less volume loading and PCC has been shown to more rapidly improve INR. However, no current studies have demonstrated improved outcome with their use and the product is far more costly. Current AHA/ASA recommendations are for either product.²²

There has been a great deal of interest in the use of recombinant factor VIIa in acute hemorrhage; however, in phase III trials, there was no improvement in outcome in patients with ICH receiving rFVIIa, and there was some increase in

arterial thrombus in the treatment arm.^{27,28} Current AHA/ASA guidelines state that there is no indication for rFVIIa in unselected patients.

MANAGEMENT OF INCREASED INTRACRANIAL PRESSURE

Patients with large intracerebral hematomas or with intraventricular involvement are at increased risk of developing increased ICP. Current AHA/ASA guidelines recommend consideration of ICP monitoring and treatment for patients with a GCS < 8, clinical evidence of transtentorial herniation, or significant IVH or hydrocephalus.²²

There are no techniques specific to the management of ICP in the subset of patients with ICH because most data have been collected from studies on patients with head injuries. Standard medical therapies include (1) maintaining head of the bed at 30 degrees; (2) optimizing analgesia and sedation, including barbiturate coma and neuromuscular blockade if needed; and (3) utilizing osmotic diuretics, such as mannitol or hypertonic saline.²⁵ Hyperventilation to a goal P_{CO_2} of 30–35 mm Hg may provide a temporary decrease in ICP, but this effect is short-lived.²⁹

Current AHA/ASA guidelines also recommend consideration of ventriculostomy with drainage of cerebrospinal fluid (CSF) as treatment for hydrocephalus in patients with decreased level of consciousness.²² Although intraventricular administration of rt-PA in patients with IVH appears to have a low complication rate,³⁰ current AHA/ASA guidelines consider this treatment investigational until the efficacy and safety have been further explored.²²

OTHER MANAGEMENT CONSIDERATIONS

It is critical to attempt to minimize secondary brain injury following ICH. Studies have shown an improved outcome in these patients when managed in a specialized neuroscience intensive care unit (NICU); as such, this is the most appropriate setting for these patients whenever possible.³¹

Admission hyperglycemia is a strong predictor of 30-day mortality in patients with ICH,^{32–34} and a randomized trial in 2001 demonstrated improved outcomes with tight glucose control (80–110 mg/dL) in surgical critical care patients.³⁵ However, more recent studies have demonstrated an increased incidence of hypoglycemic events with a possible increased risk of mortality with tight glucose control.^{36–38} Current AHA/ASA guidelines call for maintenance of euglycemia (110–150 mg/dL) and avoidance of hypoglycemia.²²

Fever has been shown to worsen outcome in patients with ICH³⁹; conversely, there is no evidence demonstrating that temperature control improves outcome in these patients. It is recommended that antipyretics and cooling blankets be employed to maintain euthermia.²²

Patients with lobar ICH are at increased risk for seizure.³⁴ Prophylactic antiepileptic medications have been shown to significantly reduce seizures in this patient population;³⁴ however, clinical seizures have not been associated with worsened outcomes or mortality.^{40–42} Therefore, prophylactic

antiepileptic medications are not currently recommended by the AHA/ASA.²² Treatment should begin if the patient has clinical seizures or in patients with changes in mental status who demonstrate seizure on electroencephalography (EEG). Continuous EEG monitoring should be considered in patients with mental status depression that is out of proportion to the degree of demonstrated brain injury. Initial management of seizures should begin with benzodiazepines such as lorazepam 0.1 mg/kg, followed by a loading dose of phenytoin or fosphenytoin (20 mg/kg).

Patients are at increased risk for thromboembolic events while under care in the NICU. It is recommended that all patients be placed in compression stockings with intermittent compression devices to the lower extremities. Small studies have found no increase in bleeding, but no difference in deep venous thrombosis (DVT) incidence, in patients given low-dose heparin initiated at day 4 or 10 post-ICH.^{43,44} Another retrospective chart review of patients with ICH who received heparin within 2 or 4 days after ICH found no significant increase in hematoma size on CT scan.⁴⁵ Current AHA/ASA guidelines recommend consideration of low-dose subcutaneous low-molecular-weight heparin or unfractionated heparin for the prevention of venous thromboembolism in patients with lack of mobility and documentation of cessation of bleeding 1–4 days post-ICH.²²

The current recommendations for surgical intervention are based largely on the STICH trial that did not confirm benefit for surgery in patients with superficial lobar hemorrhage.⁴⁶ The trial did demonstrate worsened outcome in patients with deeper hemorrhages undergoing surgery. The current AHA/ASA guidelines do recommend early surgical intervention in patients with cerebellar hemorrhage with rapid deterioration, brainstem compression, and/or hydrocephalus, and do not recommend treatment with ventricular drainage alone (Figure 34-4).²² Craniotomy may be considered in patients with large hemorrhages > 30 mL within 1 cm of the surface

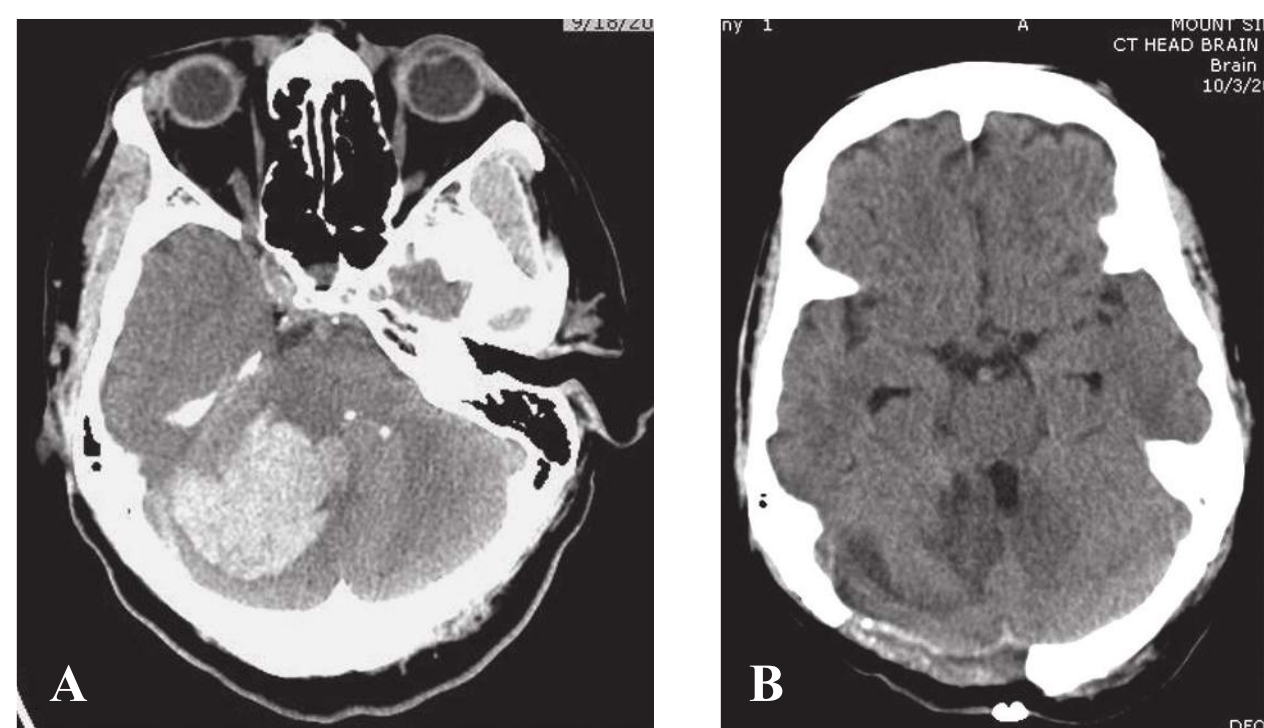


FIGURE 34-4 (A and B) Cerebellar hemorrhage and 2 weeks postoperative CT. Note the mass effect that the hematoma causes on the fourth ventricle (fully compressed) and complete effacement of the quadrigeminal plate cistern and brainstem. On the 2-week postdecompressive craniectomy follow-up CT, the fourth ventricle is again visible and the mass effect on the brainstem relieved with residual encephalomalacia in the area of hemorrhage. Immediate relief of the compressive effect of the hematoma is the objective of the surgical intervention.

of the brain. Finally, the use of minimally invasive techniques for clot evacuation is still considered investigational.

The current AHA/ASA guidelines also address the issue of mortality in patients with ICH. It is well published that the majority of patients who die from ICH will do so during their initial acute hospitalization. Newer studies that have looked at lack of intervention (do not resuscitate [DNR] orders) in the initial phase of treatment in patients with ICH have demonstrated that “early care limitations” may be an independent risk factor for mortality in this population.^{47,48} The AHA/ASA now recommends that implementation of DNR orders in patients who do not currently have them in place should not be initiated until the second hospital day.²²

SUBARACHNOID HEMORRHAGE

SAH accounts for approximately 3% of all strokes and between 1% and 3% of all patients presenting to the emergency department with the complaint of headache.^{1,49,50} While the incidence of SAH has remained relatively unchanged, mortality has significantly improved to between 25% and 45%.^{3,51} The most common cause of nontraumatic SAH is rupture of an intracranial aneurysm and will be the focus of this discussion. Numerous other causes of SAH exist, including intracranial arterial dissection, arteriovenous malformation (AVM), dural arteriovenous fistula (AVF), infectious aneurysms, infectious endocarditis, trauma, coagulation disorders, cocaine abuse, cervical origin (from a spinal AVM or AVF), cavernous malformations, vasculitis, vasculopathy, intracranial tumor, sickle cell anemia, pituitary apoplexy, and intracranial venous sinus thrombosis.

Independent risk factors for the development of SAH include female sex, hypertension, use of sympathomimetic drugs (such as cocaine), and tobacco or alcohol abuse.^{52,53} Certain genetic syndromes are also linked to formation of aneurysm and SAH. These include α_1 -antitrypsin deficiency, autosomal dominant polycystic kidney disease, type IV Ehlers–Danlos syndrome, and familial intracranial aneurysm syndrome.^{54–57} Familial intracranial aneurysm syndrome is generally defined as the presence of intracranial aneurysm in two or more siblings or three or more family members.⁵⁸ Patients with this disorder tend to have multiple aneurysms, with a 17-fold increased rupture rate than matched controls, and they suffer aneurysmal rupture at an early age.^{59–61}

Presentation and Diagnosis

The diagnosis of spontaneous SAH requires a high index of suspicion. It is estimated that approximately between 5% and 12% of patients with this type of bleed remain undiagnosed after first contact with a healthcare professional.^{62,63} Misdiagnosed patients with minimal or no neurologic deficit at initial presentation are at especially increased risk of death or disability at 1 year.⁶³

The most common presenting symptom of SAH is headache. Patients may describe the headache as the “worst headache of my life.” Patients may also present with nausea,

vomiting, neck pain, or alterations in mental status or focal neurologic deficits, frequently cranial nerve palsies.⁶⁴ It should be remembered that improvement of pain in response to conventional therapies used for headache control does *not* rule out SAH, and this thought process is a trap to be avoided.⁶⁵ Initial neurologic examination is predictive of outcome in SAH, as demonstrated by the use of validated grading scales such as the Hunt and Hess or World Federation of Neurological Surgeons.⁶⁶

The diagnosis of SAH should begin with radiographic analysis. Noncontrast CT remains the initial test of choice, with a sensitivity of at least 97% in the first 6 hours following headache onset.⁶⁷ Sensitivity declines as the time since headache onset elapses. CTA may be helpful in the identification of aneurysm and is highly sensitive for aneurysms > 3 mm; however, sensitivity is low in detecting smaller aneurysms.^{68,69} Magnetic resonance imaging (MRI) may also be helpful in identifying cerebral aneurysm, but is generally considered a secondary imaging modality usually due to cost and time restraints.⁶⁶

For these reasons, the gold standard used to rule out SAH in patients with suspected SAH and nondiagnostic imaging remains the lumbar puncture (LP).^{65,66} When properly performed and interpreted, the sensitivity of an LP in combination with a negative head CT approaches 100% with a 99% negative predictive value.⁷⁰ However, the interpretation of LP data, specifically in regard to xanthochromia and the number of red blood cells (RBCs) required to diagnose SAH, remains an area of research. Xanthochromia describes the yellowish discoloration of the cerebrospinal fluid supernatant seen secondary to RBC lysis and is diagnostic of SAH. However, it may take up to 12 hours for RBCs to lyse sufficiently to produce this finding. Additionally, although spectrophotometry is considered standard of care for the diagnosis of xanthochromia in the United Kingdom, the diagnosis of xanthochromia in the United States is made solely on visual inspection. Whether spectrophotometry or visual inspection is the most appropriate method for the detection of xanthochromia is under discussion.^{71,72}

There is no clear guideline for the number of RBCs required to diagnose SAH on LP because it can be difficult to distinguish a traumatic tap from a true SAH. A decrease in the number of RBCs between the first and fourth tubes collected has been thought to be indicative of a traumatic tap instead of SAH. However, studies have found SAH even in the presence of a > 25% decrease in RBCs between the first and last tubes.^{73,74} In most studies, < 100 RBCs in the final tube has been shown to effectively rule out SAH, whereas > 10,000 RBCs in the final tube has been shown to significantly increase the odds of SAH.^{74,75}

Treatment of Aneurysmal Subarachnoid Hemorrhage

The object of aneurysmal SAH treatment is to prevent rerupture of the aneurysm. Aneurysm rebleeding is associated with high mortality and poor prognosis for functional

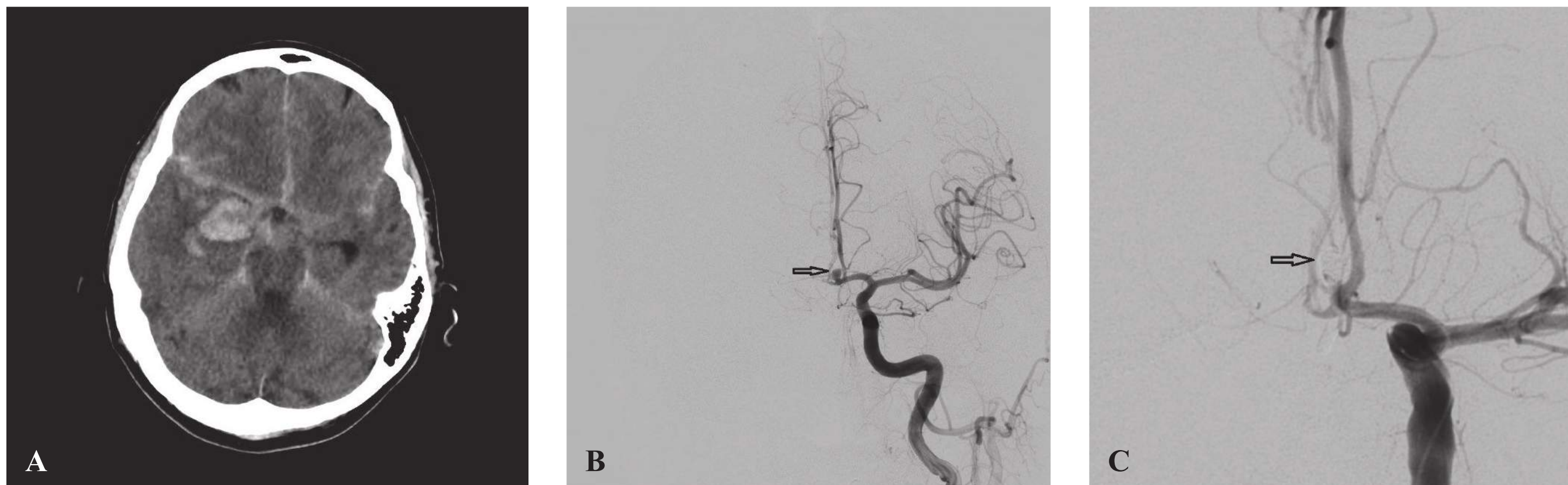


FIGURE 34-5 (A–C) CT scan demonstrates diffuse subarachnoid hemorrhage. CTA demonstrates an anterior communicating artery aneurysm pointing right and upward. This is confirmed on cerebral angiography. Post-aneurysm coil embolization angiogram is demonstrated. Note the lack of filling within the aneurysm.

recovery.^{66,76} The risk of rebleeding is highest within the first 6 hours, with reported rates of between 4% and 14% within the first 24 hours.^{66,77,78} If left untreated, there is a 50% risk of rerupture in the first 6 months.⁷⁶ Early treatment (within 48 hours) is recommended to prevent the high mortality rate associated with rebleeding.⁶⁶ Securing an aneurysm may be performed either by open microsurgical technique (clipping) or via endovascular technique (coiling) (Figure 34-5).

The international subarachnoid aneurysm trial (ISAT) randomized 2,143 spontaneous SAH patients to clipping versus coiling within 28 days of SAH ictus. Although the study has been criticized, disability-free survival was significantly better with endovascular coiling versus surgical clipping at 1 year.⁷⁹ At 7-year follow-up, the significant difference in disability-free survival was maintained between the two groups. The risk of epilepsy was significantly lower in the endovascular group, but the risk of late rebleeding was higher.⁸⁰ The optimal method of treatment remains individualized for each patient depending on aneurysm morphology, location, and patient characteristics, but for patients with ruptured aneurysms judged to be technically amenable to both endovascular coiling and neurosurgical clipping, the AHA/ASA guidelines recommend consideration of endovascular coiling.⁶⁶

Medical Management of Subarachnoid Hemorrhage

Patients requiring airway or ventilatory support should be managed as in the prior discussion of patients with ICH. All patients with SAH are best served by admission to an NICU preferably in a facility with access to experts in neurovascular interventional care.⁶⁶ The two major goals in the medical management of patients with SAH are to prevent rebleeding and limit vasospasm in the cerebral circulation.

Factors associated with rebleeding include larger aneurysm size, poor neurologic status upon admission, initial loss of consciousness, and SBP > 160 mm Hg.^{76–78} The AHA/ASA recommends that acute hypertension should be controlled

until the ruptured aneurysm has been obliterated via coiling or clipping, but parameters for BP control have not been defined. Current guidelines state that a decrease in SBP to < 160 mm Hg is reasonable and recommend using a titratable agent such as nicardipine or labetalol.⁶⁶ The use of antifibrinolytics to prevent aneurysmal rebleeding is currently under investigation.^{81–83} For patients with an unavoidable delay in obliteration of an aneurysm, a significant risk of rebleeding, and no compelling medical contraindications, the AHA/ASA recommends that a short-term (< 72 hours) therapy with tranexamic acid or aminocaproic acid is reasonable to reduce the risk of early aneurysm rebleeding.⁶⁶

Cerebral artery vasospasm with subsequent delayed cerebral ischemia (DCI) is a major cause of morbidity and mortality in patients with SAH. Risk factors for vasospasm include thick blood on CT, cigarette smoking, hypertension, and poor neurologic status.^{84–86} Vasospasm most commonly occurs between 7 and 10 days after aneurysm rupture and resolves spontaneously after 21 days.⁶⁶ Angiographic evidence of vasospasm can be seen in 30–70% of patients after SAH, but only half of these patients will demonstrate neurologic deficits.^{87,88} Up to 20% of these patients will suffer permanent ischemic infarction or die.^{89,90} Nimodipine, a calcium channel antagonist, has been shown to improve neurologic outcomes and reduce the occurrence of vasospasm, and the AHA/ASA recommends that oral nimodipine be administered to all patients with SAH.^{91,92} Current guidelines also recommend the maintenance of euvolemia and normal circulating blood volume to prevent vasospasm and DCI.⁶⁶

The diagnosis of DCI can be difficult, especially in patients with poor neurologic status. Changes in blood flow velocity, especially in the middle cerebral artery, can be measured by transcranial Doppler, and AHA/ASA guidelines state that it is reasonable to use transcranial Doppler to monitor for the development of arterial vasospasm.^{66,93} Perfusion imaging with CT or MR can also be useful to identify regions of potential brain ischemia.^{66,94} Once DCI is identified, hemodynamic augmentation should be initiated to improve

cerebral perfusion. This augmentation has traditionally consisted of hemodilution, hypervolemia, and hypertensive therapy—collectively called “triple-H therapy.” However, no randomized trials of these interventions have been performed. Due to the findings of recent studies focusing on euvolemia and induced hypertension, the AHA/ASA recommends induction of hypertension for DCI unless the patient is hypertensive at baseline or cardiac status precludes it.^{66,95,96} Endovascular interventions with balloon angioplasty and/or intra-arterial delivery of vasodilators, usually calcium channel blockers, are often used for patients who do not improve with hemodynamic augmentation or those with sudden focal deficits and lesion on angiography.⁹⁷

Finally, patients with SAH are at risk for other complications, including hyperglycemia, hyperthermia, seizure, DVT, hydrocephalus, and hyponatremia. Hyperglycemia is associated with poor clinical outcomes in patients with SAH.⁹⁸ AHA/ASA guidelines recommend careful glucose management with strict avoidance of hypoglycemia.⁶⁶ Fever is the most common medical complication of SAH and has been associated with severity of injury, amount of hemorrhage, and development of vasospasm.^{99–101} Fever is also independently associated with worse cognitive outcome and mortality in SAH, with improved functional outcome demonstrated with effective control of fever.^{101–103} Aggressive control of fever to a target of normothermia by use of temperature-modulating systems is reasonable in the acute phase of SAH.⁶⁶

Prophylactic use of anticonvulsants in SAH remains controversial but may be considered in the immediate posthemorrhagic period.⁶⁶ Seizures in SAH should be managed as with seizures from any cause, first with lorazepam or another benzodiazepine followed by anticonvulsants such as phenytoin or fosphenytoin. Patients with SAH are at increased risk for DVT, with an incidence of 18% in one recent cohort study.¹⁰⁴ Compression stockings and intermittent compression devices should be used to prevent the development of DVT. Subcutaneous administration of anticoagulants may be used once the aneurysm is safely secured.

External ventricular drains (EVD) should be placed in patients with hydrocephalus or evidence of increased ICP. Acute hydrocephalus occurs in 15–87% of patients with SAH and is usually managed with EVD or lumbar drainage.⁶⁶ Appropriate analgesia and antiemetics may also prevent increased ICP.

Finally, hyponatremia occurs in between 10% and 30% of all patients with SAH and has been associated with clinical vasospasm.^{66,105,106} Hyponatremia can result from multiple different mechanisms after SAH. Cerebral salt wasting (CSW) is thought to result from excessive central secretion of natriuretic peptides causing hyponatremia and volume contraction from excessive renal salt wasting. Conversely, patients with syndrome of inappropriate antidiuretic hormone (SIADH) will usually presents as normo- or hypervolemic with concentrated, low urine output. Fludrocortisones have been shown to correct hyponatremia and fluid balance in SAH.^{107–109} Hypertonic saline solution can also be used.¹¹⁰ Care must be taken not to correct hyponatremia too quickly (> 8 mEq/L/day)

because this may lead to central pontine myelinolysis. However, this is rare in patients with hyponatremia of < 24 hours duration. Current AHA/ASA guidelines state that the use of fludrocortisones and hypertonic saline solution is reasonable for preventing and correcting hyponatremia.⁶⁶

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Traumatic Brain Injury

Daniel J. Haase • Deborah M. Stein

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INTRODUCTION

Epidemiology

The Centers for Disease Control and Prevention (CDC) estimates that at least 2.4 million people sustained a traumatic brain injury (TBI) in 2009.¹ However, the actual number of TBI cases is uncertain as many patients either receive care in the field or do not seek medical attention at all because approximately three-quarters of TBI are mild or concussions.²

The causes of TBI in all age groups combined are falls (35.2%), motor vehicle accident (17.3%), being struck by or running into an object (16.5%), assault (10%), and other or unknown causes (21%).³ Among all age groups, males have higher incidences of TBI and on average present with TBI about 1.4 times more frequently than females. The CDC identified three age groups—children (0–4 years), adolescents (15–19 years), and adults (65 years and older)—as most likely to sustain TBI.³ Children aged 0–4 years had the highest rate of TBI-related emergency department visits (1,256 per 100,000 population). However, the elderly (75 and older) had highest hospitalization (339 per 100,000 population) and death (57 per 100,000 population).³ TBI-related death rates have substantially declined in the past 30 years, and this can mostly be attributed to primary prevention. Motor vehicle-related TBI deaths declined 22% and firearm-related TBI deaths declined 14% between 1989 and 1998,⁴ but declines in death rates since that time have been more modest.⁵

The economic costs of TBI in 2010 was estimated at \$76.5 billion, \$11.5 billion from direct medical costs and the remaining \$64.8 billion from indirect costs (e.g., lost wages, productivity). These data do not include the more than 31,000 military personnel who were seen in the Veterans

Administration for TBI-related medical issues in 2010.⁶ An estimated 5.3 million Americans are living in with TBI-related physical, cognitive, or psychological impairments.⁷

PATHOPHYSIOLOGY

An appreciation for the pathophysiologic mechanisms at work after TBI is important for the development and implementation of effective clinical therapeutic strategies. The injury due to TBI can be understood in terms of primary and secondary insults to neural tissue. Primary injury denotes the initial mechanical damage secondary to energy transmission during impact, whereas secondary injury results from the destructive tissue-intrinsic and body systemic response to primary injury. Primary injuries cannot be altered after the fact but can be reduced using primary prevention (seatbelts, helmets, etc.) and are the target of public health intervention.

Secondary injury includes edema and inflammation from the primary insult and the insults thereafter. Secondary injury can be caused by alterations in perfusion such as ischemia, hyperemia, or vasospasm, as well as by expanding hemorrhage, hypoxia, hypotension, seizures, and metabolic derangements such as hyper-/hypoglycemia and hyponatremia. Detailed accounts of the molecular and cellular mechanisms of TBI have been proposed.^{8–10} The foundation of TBI care is based in prevention and modification of secondary injury.¹¹

INITIAL ASSESSMENT

The initial assessment of neurotrauma patients should begin with the familiar ABCs of trauma resuscitation: evaluate the airway, confirm breathing with effective ventilation, and assess

**TABLE 35-1: Glasgow Coma Scale**

Points	Eye Opening	Verbal Response	Motor Response
6	—	—	Obeys commands
5	—	Oriented	Localizes to pain
4	Spontaneous	Confused	Withdraws to pain
3	To speech	Inappropriate	Flexor posturing
2	To pain	Incomprehensible	Extensor posturing
1	None	None	None

the circulatory status. Cervical hard collar placement and body immobilization on a rigid backboard is warranted for all blunt trauma patients, despite recent literature calling it into question. Clinically deteriorating patients and those with a Glasgow Coma Scale (GCS) score of ≤ 8 should be intubated because they are unable to adequately protect their airway. Precautions such as logrolling and inline stabilization during intubation are prudent until spinal stability is verified.¹² Cardiac, hemodynamic, respiratory, and pulse oximetry monitoring is necessary for all patients with moderate and severe TBI.^{11,12} Hypoxemia ($\text{SaO}_2 < 90\%$) and hypotension (systolic blood pressure < 90 mm Hg) should be avoided in TBI, as outcomes have clearly been shown to be worse if hypoxia or hypotension is present.^{11,13} Intubation, volume resuscitation with intravenous fluids or transfusion, and the use of vasopressor medications may be necessary to achieve these initial goals.

Visual inspection of the general physical condition of the patient should be carried out. Evidence of basal skull fracture (periorbital or postauricular ecchymoses, cerebrospinal fluid CSF rhinorrhea/otorrhea), facial fracture, or spine deformity should be noted. At a minimum, the initial neurologic examination should encompass assessment of the following:

- Level of consciousness with a determination of the GCS (Table 35-1)
- Cranial nerve (CN) function with particular attention to the size, symmetry, and reactivity of pupils
- Gross motor and sensory examination of the extremities

In cases of suspected spinal cord injury, a more detailed motor exam and determination of a specific sensory level is appropriate. Additionally, a digital rectal exam checking for voluntary anal sphincter contraction should be performed, and an American Spinal Injury Association (ASIA) impairment scale grade (see below) should be assigned.¹²

While in the acute period, all patients with TBI should be neurologically examined on a regular basis—at least every hour for the first 24 hours (hyperacute period) and then less often as clinically indicated. In general, cerebral edema is greatest from 48 to 96 hours following injury. Thereafter, edema resolution ensues, with most patients showing some measure of clinical improvement.

Clinical Severity of Brain Injury

Patients with a GCS of ≤ 8 are considered to have severe TBI and will require advanced medical care in the prehospital

setting as well as neurocritical care management. Severe TBI is associated with significant neurologic injury, often with structural lesions revealed by neuroimaging (e.g., head computed tomography CT scan revealing skull fracture, intracranial hemorrhage, and early diffuse cerebral edema). After initial resuscitation and stabilization in the field, patients with severe TBI should be evacuated to the nearest Level 1 trauma center with neurosurgical capability. Patients presenting with moderate TBI (GCS 9–12) should also be treated in the critical care setting, whereas those with mild TBI (GCS 13–15) may or may not require hospital admission.^{14–17}

It should be noted that in addition to the GCS parameter, mild TBI is formally defined as the presence of loss of consciousness for ≤ 30 minutes, post-traumatic amnesia not greater than 24 hours, any alteration in mental status at the time of injury, or focal neurologic deficit.¹⁸ In clinical practice, concussion and mild TBI are often used interchangeably; however, the terms are subtly distinct if only because they were independently defined by different expert panels. The American Academy of Neurology (AAN) defines concussion as a trauma-induced alteration in mental status with confusion and amnesia being the hallmarks.¹⁹ Because the GCS does not provide enough detail to give a useful clinical picture in cases of mild TBI or concussion, a variety of scales have been developed (Table 35-2).^{19,20}

**TABLE 35-2: Cantu and American Academy of Neurology (AAN) Concussion Grading Scales**

Grade	Cantu	AAN
1	a. No LOC b. PTA < 30 min	a. No LOC b. Transient confusion c. Symptom resolution in < 15 min
2	a. LOC < 5 min b. PTA > 30 min (< 24 h)	a. No LOC b. Transient confusion c. Persistent symptoms > 15 min
3	a. LOC > 5 min b. PTA > 24 h	a. Any LOC

LOC, loss of consciousness; PTA, post-traumatic amnesia.



TABLE 35-3: Marshall Classification of Diffuse Brain Injury

Category	Features on Noncontrast Head CT	Outcome at Discharge ^a
Diffuse injury I	a. No pathology	27% good 34.6% moderate
Diffuse injury II	a. Midline shift 0–5 mm with visible basal cisterns b. No high or mixed density lesion > 25 cm ³	8.5% good 26% moderate
Diffuse injury III	a. Midline shift 0–5 mm with cisterns compressed or absent b. No high or mixed density lesion > 25 cm ³	3.3% good 3.1% moderate
Diffuse injury IV	a. Midline shift > 5 mm b. No high or mixed density lesion > 25 cm ³	3.1% good 3.1% moderate

^aData from Marshall L, Marshall S, Klauber M, et al: A new classification of head injury based on computerized tomography, *J Neurosurg* 1991; 75(suppl):S14–S20.

RADIOGRAPHIC EVALUATION AND CLASSIFICATION

Head Injury Imaging

A noncontrast head CT should be the initial imaging modality used to evaluate TBI patients. Criteria for performing head CT in patients with mild TBI have been suggested (e.g., New Orleans and Canadian Head CT rules).^{21,22} A recent validation showed that the Canadian head CT rule was more sensitive than the New Orleans rule for detecting both a positive head CT and the need for neurological procedure.²³ The Marshall CT classification that segregates diffuse brain injury into several categories is often a helpful prognostic guide (Table 35-3), but its current use is not widespread.²⁴

In cases of penetrating brain injury, CT angiography or conventional angiography should be performed when injury to a major vessel is suspected.²⁵ While the true incidence of vascular injury (e.g., dissection, thrombosis, pseudoaneurysm) in PBI is unknown, it is reasonable to evaluate the cerebral vasculature when the patient is hemodynamically stable. Brain magnetic resonance imaging (MRI) is generally not indicated in the acute setting, but may be helpful for further assessment and prognostication later during the patient's hospital course.

Epidural Hematoma

An acute epidural hematoma (EDH) occurs when blood collects between the dura mater and the inner table of the skull. Although these account for a small amount of trauma admissions, they have a relatively high morbidity and mortality because most EDHs are due to arterial bleeding of the middle meningeal artery.

EDH classically occurs with a brief loss of consciousness, followed by a lucid interval of minutes to hours, followed by an acute decompensation in neurological status. This presentation is commonly referred to as the “talk and die” syndrome.

On head CT, an EDH appears as a biconvex or lens-shaped mass lesion, located between the skull and the brain. These classically do not cross suture lines. Surgical evacuation should be considered in EDHs with a volume > 30 mL regardless of the patient's GCS score. In patients with severe TBI, pupillary abnormalities, or other focal neurologic deficits, a

craniotomy for evacuation should occur as soon as possible. An EDH with volume of < 30 mL, thickness < 15 mm, and midline shift < 5 mm in a patient with GCS > 8 and no focal deficits may be managed nonoperatively with serial head CT and close observation.²⁶

Subdural Hematoma

An acute subdural hematoma (SDH) occurs when blood collects between the inner layer of the dura mater and the arachnoid space. These are classically due to injury of the bridging cortical veins. SDH is more common in the elderly due to increased atrophy.

SDH can present in a variety of ways, even with indolent progression over days to weeks. Compared to EDH of similar size, SDH has a higher mortality mostly postulated because of increased force required to cause an SDH and subsequent injury to underlying brain. For all SDHs, mortality may be as high as 90%, but can be improved with early intervention.^{27,28}

Surgical evacuation is indicated with SDH thickness > 10 mm or midline shift > 5 mm, regardless of the patient's GCS score. If the patient is comatose (GCS < 9) and has pupillary abnormality or ICP > 20 mm Hg or had a clinical decline by 2 or more GCS points, hematoma evacuation as soon as possible is also indicated.²⁶

Parenchymal Lesions and Diffuse Injury

Traumatic parenchymal lesions include both focal and nonfocal lesions. The focal lesions occur at the site of impact (coup) or opposite the site of impact (contrecoup) and include intracerebral hematoma (ICH), contusion, and infarction. Nonfocal lesions include diffuse injury typically resulting in hemispheric or global cerebral edema.

Patients with traumatic parenchymal mass lesions causing neurologic deterioration, refractory intracranial hypertension, or evidence of mass effect on CT should be treated surgically. Similarly, any lesion > 50 mL should be evacuated. In patients with GCS 6–8, a lesion > 20 mL should be evacuated if it is frontal or temporal in location and causing > 5 mm of midline shift and/or cisternal compression.²⁶ Contusions commonly affecting the orbitofrontal and anterior temporal lobes

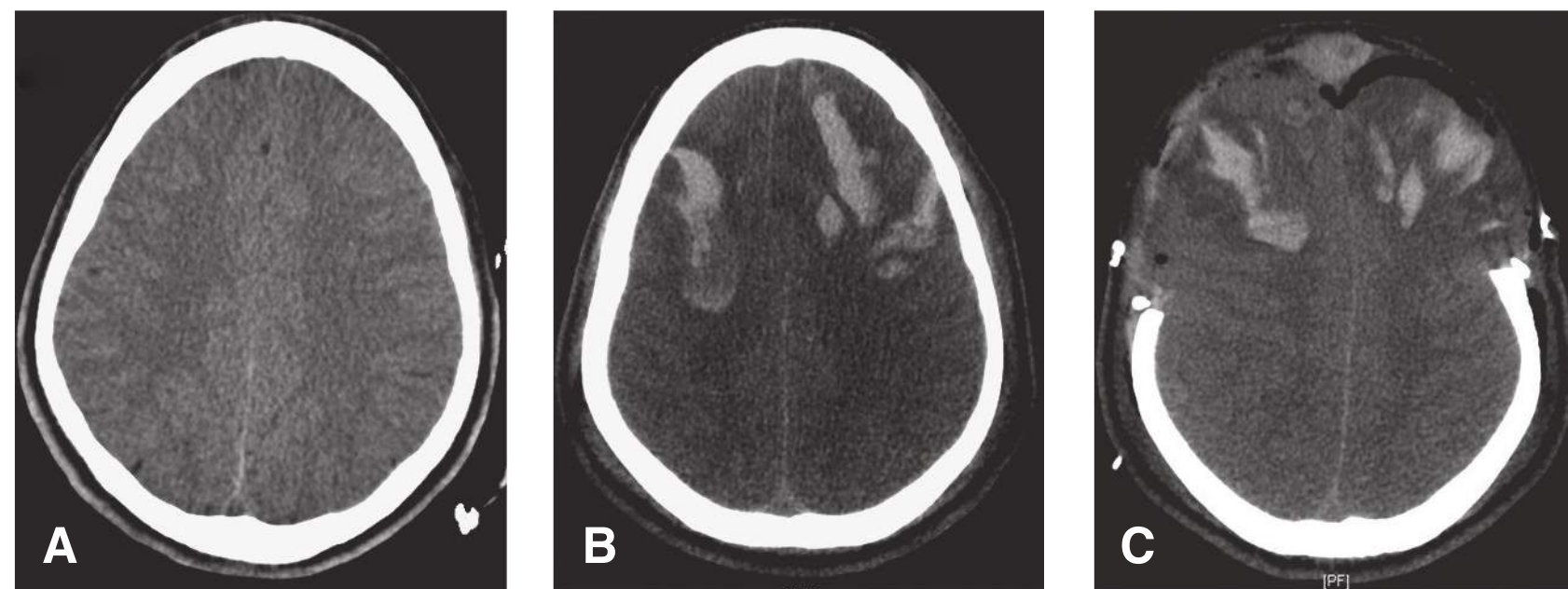


FIGURE 35-1 Intracerebral hematoma expansion within bifrontal contusions. This 27-year-old male patient presented with a GCS score of 3 after being ejected head first from a motorcycle during a collision. Initial noncontrast head CT was significant for bilateral frontal lobe contusions with early evidence of sulcal effacement (**A**). A follow-up noncontrast head CT performed 9 hours after initial presentation showed the interval development of large bilateral intraparenchymal hemorrhages (**B**). The patient subsequently developed refractory intracranial hypertension necessitating performance of a bilateral frontotemporal craniectomy with duraplasty for ICP control (**C**).

must be observed with particular vigilance. Delayed hematomas that can manifest or “blossom” within hours to days may require urgent craniectomy (Figure 35-1).

The recent DECRA trial has stirred significant controversy regarding decompressive craniectomy for severe diffuse TBI.²⁹ The study demonstrated worse outcomes in patients receiving decompressive craniectomy, but the groups were unequal at randomization, the surgical technique was not standard, and the indications for surgery were quite liberal. Furthermore, this study included decompression for mass lesions. Many experts feel the results of this study are unable to be generalized and believe that decompressive craniectomy is still a potential therapy for patients with refractory elevated high ICP. A study that has recently concluded (RESCUE-ICP), but with results not yet released, may provide more answers to this controversy. Decompressive craniectomy for refractory high ICP is discussed further later in the chapter.

Posterior Fossa Mass Lesions

A traumatic posterior fossa mass lesion should be evacuated by suboccipital craniectomy if there is radiographic evidence of mass effect or if neurologic dysfunction is referable to the lesion. Because neurologic decline can be precipitous in patients with these lesions, due to either direct midbrain compression causing respiratory compromise or obstruction of the fourth ventricle leading to acute hydrocephalus, surgery should be performed as soon as possible.²⁶

Depressed Cranial Fractures

Closed (simple) nondepressed, typically linear, cranial fractures are not surgical lesions unless associated with an intracranial mass. On the other hand, depressed cranial fractures



FIGURE 35-2 Left epidural hematoma with local mass effect.

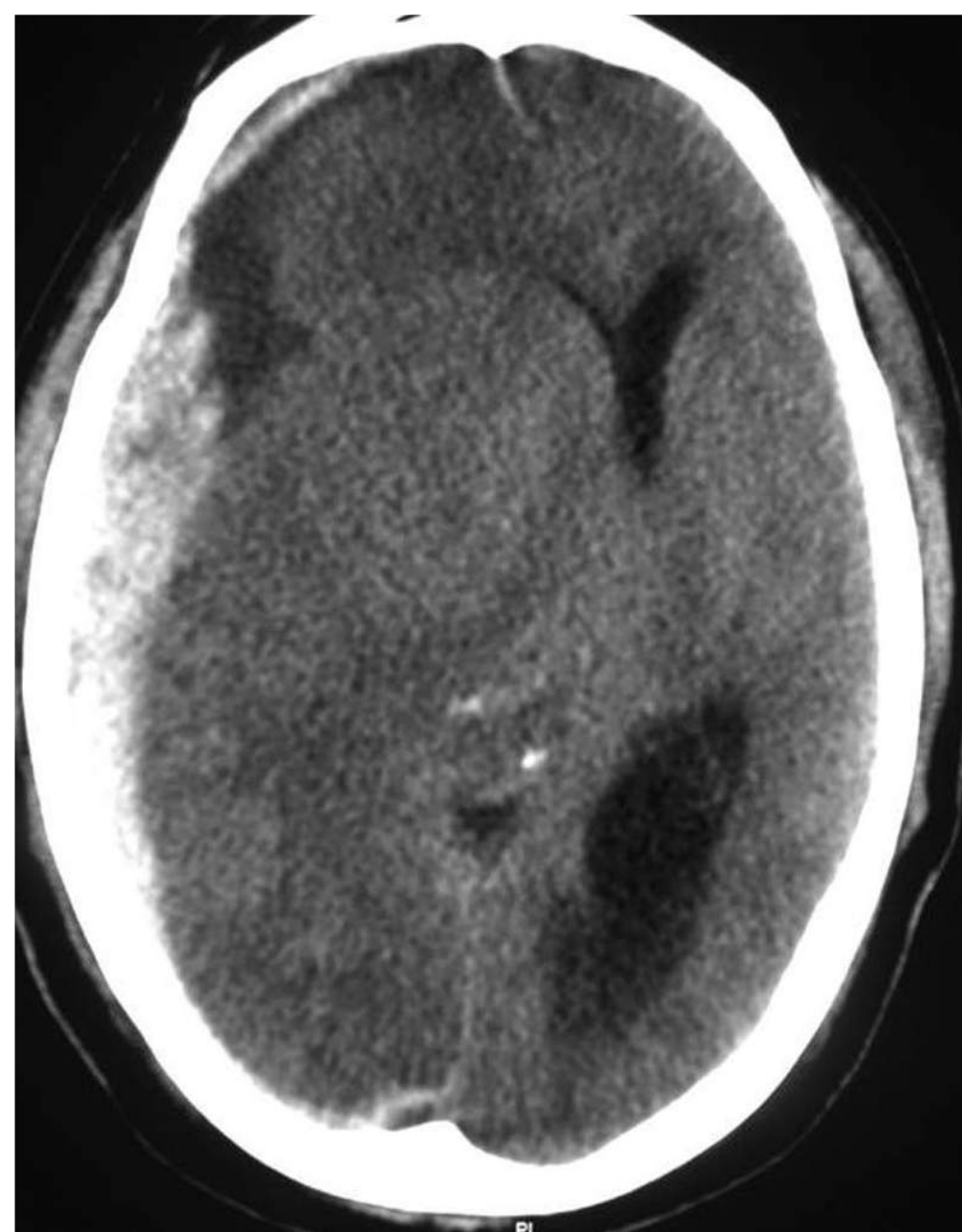


FIGURE 35-3 Large right subdural hematoma with significant midline shift and hydrocephalus.

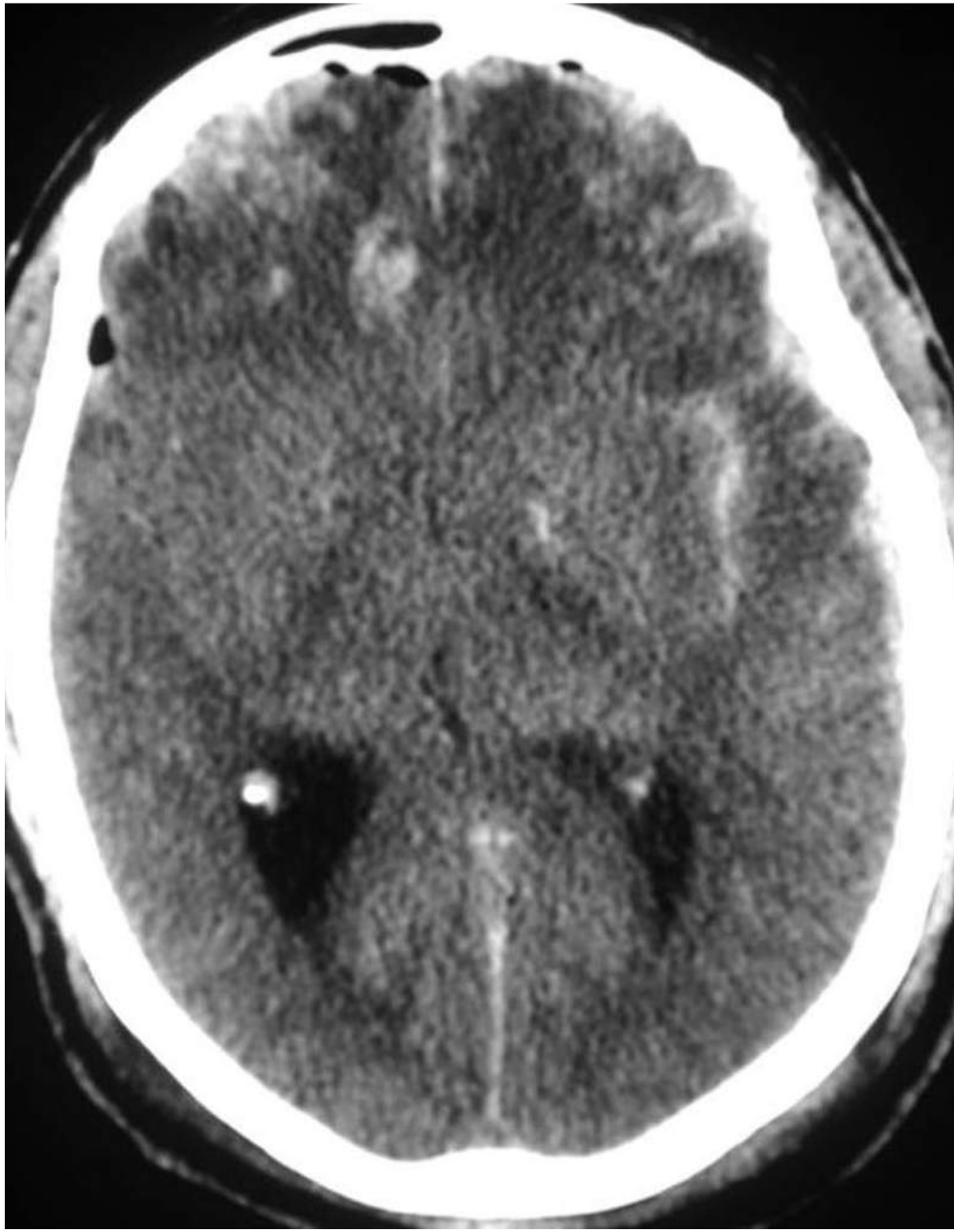


FIGURE 35-4 Bilateral frontal contusions with scattered subarachnoid hemorrhage.

may be managed either surgically or nonsurgically depending on the particular case.

Patients with open (compound) cranial fractures depressed greater than the thickness of the cranium should undergo early elevation of the bone fragments and debridement of the wound. Open cranial fractures with depression of < 1 cm and with no dural penetration, significant intracranial hematoma,

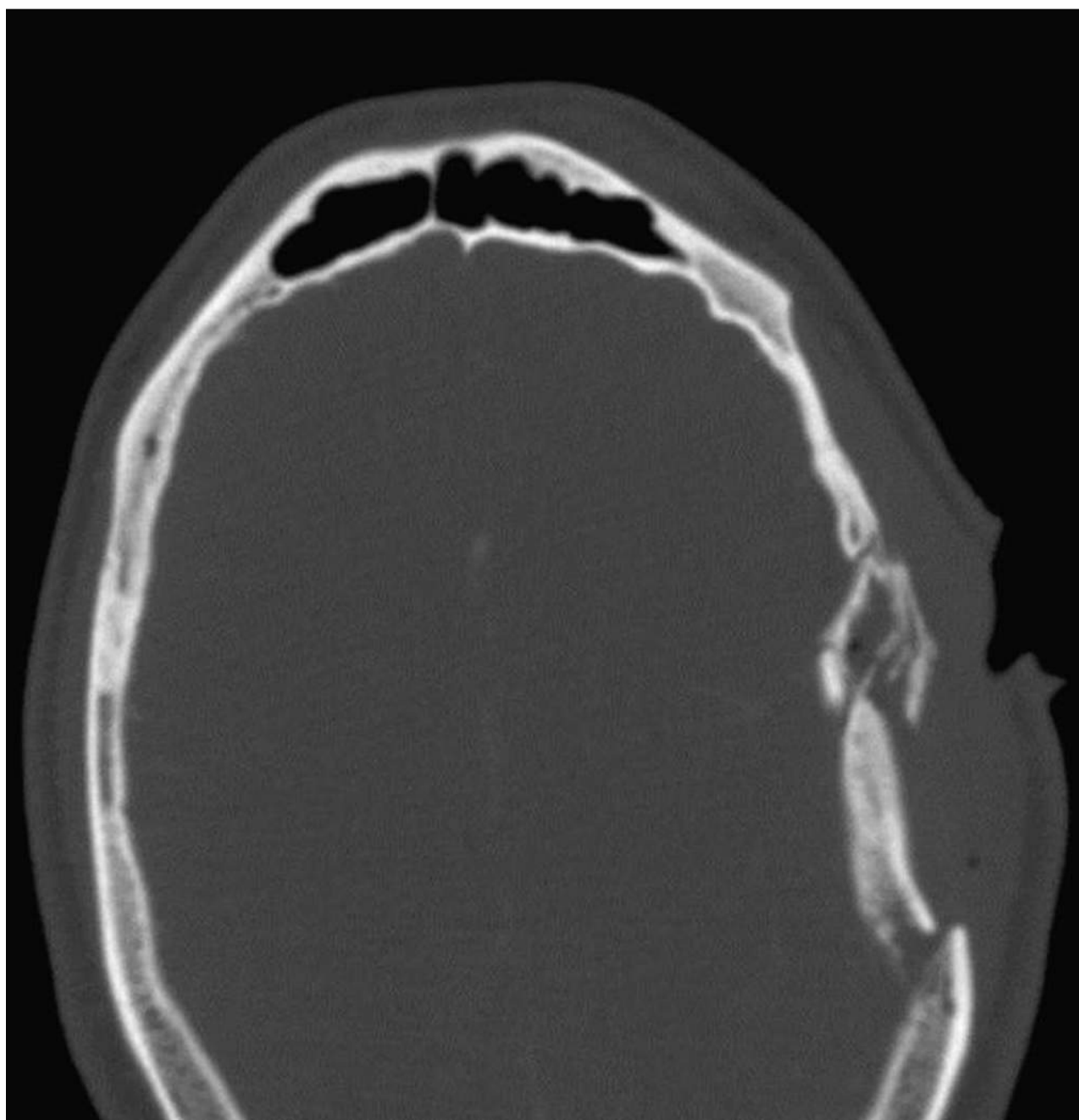


FIGURE 35-5 Left comminuted and depressed skull fracture.



FIGURE 35-6 Diffuse axonal injury with scattered punctate hemorrhages.

frontal sinus involvement, gross deformity, wound infection, pneumocephalus, or gross wound contamination may be treated nonoperatively. Evaluation of the fracture in proximity to dural sinus must be considered, and is a relative contraindication to surgery. Furthermore, dural sinus thrombosis may occur and should be evaluated by CT venogram if clinically warranted.²⁶

Although not rigorously supported in the literature, closed depressed cranial fractures are often surgically treated if the extent of depression is greater than the thickness of the adjacent calvarium to effect better cosmesis and lower rates of post-traumatic seizure (PTS) and neurologic deficit. Nonoperative management, however, is a treatment option in these cases.²⁶

Penetrating Brain Injury

Penetrating brain injury involves both missile and nonmissile trauma to the brain. No strict guidelines dictate when surgical debridement, hematoma evacuation, and/or removal of protruding foreign body are warranted. In one study of gunshot wounds to the head, it was suggested that all patients with GCS 9–15 should have aggressive surgical therapy; patients with GCS 6–8 should have surgical therapy if no transventricular, multilobar, or dominant hemisphere injury is present; and patients with GCS 3–5 should have surgical therapy only if a large extra-axial hematoma is present.^{26,30}

Broad-spectrum antibiotic prophylaxis should be administered, with the most common regimen being vancomycin, ceftriaxone, and metronidazole.³⁰ Although duration is unclear, there seems to be little benefit for longer duration of therapy, and we favor a short course of prophylactic antibiotics to prevent anti-microbial resistance.³¹



FIGURE 35-7 Ballistic fragment with scatter artifact and local swelling. Intraventricular hemorrhage is present on left.

INTENSIVE CARE MEASURES

No discrete segregation exists between the emergency care, the surgical care, and the critical care of neurotrauma patients. The intensive care management of TBI patients begins in the field with first responders and continues until the patient is stable for intensive care unit (ICU) discharge. At all phases of care, the goal is to prevent secondary brain injury. The recommendations are set forth in the Brain Trauma Foundation's *Guidelines for the Management of Severe Traumatic Brain Injury*.¹¹ Additional guidelines have been released by the Brain Trauma Foundation in an attempt to optimize pre-hospital and neurosurgical care.^{26,33}

Blood Pressure and Oxygenation

As previously discussed, both hypotension (systolic blood pressure < 90 mm Hg) and hypoxia (SaO_2 < 90% or PaO_2 < 60 mm Hg) should be avoided as outcomes are significantly worse even with a single episode of hypotension or hypoxia.¹¹ In severe TBI, we recommend the placement of an arterial catheter for continuous blood pressure measurement and central venous access (with the preferred site being subclavian vein) for medication administration and fluid resuscitation.

Intracranial Pressure Monitoring and Cerebral Perfusion Pressure

A number of devices are available for ICP monitoring. Intraventricular drains provide the most accurate and reliable measurements of ICP and also allow for therapeutic drainage of CSF. However, in the setting of global cerebral edema

with collapse of the lateral ventricles, ventriculostomy may not be possible. Parenchymal ICP monitors are also accurate and useful when ventriculostomy is not possible but their inability to effect CSF diversion makes them less ideal. Subarachnoid, subdural, and epidural ICP monitors are the least favored devices.¹¹

ICP monitoring is frequently initiated in severe TBI (GCS 3–8) patients and in select patients with GCS > 8 whose neurologic exam cannot be followed. The guidelines recommend ICP monitoring in survivable severe TBI ($\text{GCS} \leq 8$) patients with either¹¹:

- (1) An abnormal head CT or
- (2) A normal head CT and two or more of the following:
 - (A) Age > 40 years
 - (B) Motor posturing
 - (C) Systolic blood pressure < 90 mm Hg

Cerebral perfusion pressure (CPP) is defined as the difference between the mean arterial pressure (MAP) and the ICP. CPP maintenance is an important clinical parameter that can be used to prevent the reductions in CBF that are associated with poor outcome. In patients with brain injury, cerebral vasculature loses its ability to autoregulate, thus necessitating more invasive monitoring and intervention. While the literature points to no clear optimal CPP target, multiple studies suggest maintenance within the range of 50–70 mm Hg with a goal of 60 mm Hg for the severe TBI population.¹¹ CPP < 50 and > 70 mm Hg is associated with higher morbidity and mortality.¹¹ CPP can be defined as:

$$\text{CPP} = \text{MAP} - \text{ICP}$$

A recent article was published comparing an invasive ICP monitoring protocol versus a protocol using strictly imaging and clinical exam.³⁴ While the ICP monitoring group did not show a statistically significant benefit, there was a trend in that direction. Furthermore, the imaging group had more interventions (e.g., hyperosmolar therapy, hyperventilation) than the ICP monitoring group. This article calls into question the benefit of ICP monitoring but has not changed the standard of care, and a recent conference of experts concluded that ICP monitoring has the potential to benefit outcome; further investigation is needed.³⁵

Brain Oxygen Monitoring

Low brain oxygenation as measured globally by jugular venous oxygen saturation ($\text{S}_{\text{JV}}\text{O}_2$) or locally by brain tissue oxygen tension ($\text{P}_{\text{bt}}\text{O}_2$) is associated with poor outcomes.¹¹ Desaturations of $\text{S}_{\text{JV}}\text{O}_2$ to values of < 50% have been shown to indicate various ischemia-inducing pathologies such as elevated ICP, hypocarbia, arterial hypoxia, systemic hypotension, and cerebral vasospasm. Sheinberg et al. showed a trend toward increasing death rates in TBI patients who had multiple $\text{S}_{\text{JV}}\text{O}_2$ desaturations.³⁶ Similarly, the length of time $\text{P}_{\text{bt}}\text{O}_2$ levels were < 15 mm Hg is also associated with increased death rates.³⁷ In a recent retrospective series, TBI patients managed with $\text{P}_{\text{bt}}\text{O}_2$ -directed therapy had better outcomes than patients

managed with standard ICP/CPP-directed therapy.³⁸ Interestingly, elevated $S_{jv}O_2$ levels ($> 75\%$) are associated with poor outcomes and may be an indication of hyperemia or infarction.³⁹ Therefore, brain oxygen monitoring not only gives information on brain state but also provides another parameter that can be clinically optimized.

Controlling Intracranial Pressure

Consensus recommendations based on class II evidence suggest that treatment for ICP should be initiated for sustained values > 20 mm Hg.¹¹ Nonetheless, it is important to remember that absolute values of ICP and CPP may not correlate with a patient's clinical status, and deterioration in status should prompt further investigation and intervention, even if ICP is not elevated. The methods here detail an approach to the treatment of intracranial hypertension in neurotrauma patients (Table 35-4). At all stages during the escalation of ICP-lowering therapy, a high suspicion for enlarging mass lesion must be entertained with a low threshold for obtaining a head CT (Table 35-5). Electroencephalography (EEG) should also be considered because seizures can be a cause of refractory high ICP.

GENERAL MEASURES

The general measures used for decreasing ICP include ensuring neutral head and neck position, elevating the head of bed (HOB) to 30–45 degrees, providing adequate sedation and analgesia, and avoiding fever. A neutral head position allows for unimpeded venous drainage out of the intracranial compartment, thus decreasing cerebral blood volume and ICP. Keeping the HOB elevated at 30–45 degrees also enhances venous outflow using gravity. Because fever is known to increase both the cerebral metabolic rate and ICP, maintenance of normothermia along with the prevention of shivering is important. Although TBI alone can induce a fever, this should be a diagnosis of exclusion. Febrile patients must be appropriately assessed for underlying infection with tests including complete blood count, chest x-ray, urinalysis, and cultures of blood and urine. Fever reduction can be achieved with acetaminophen, cooling blankets or vests, or intravascular devices. If a patient develops severe shivering, one should consider administering meperidine, buspirone, magnesium; counter-warming; or increasing sedation with or without pharmacologic paralysis.

FIRST-LINE THERAPIES

Sedation and analgesia: Agitation, discomfort, endotracheal tube-induced coughing, tensing the abdominal musculature, and elevated sympathetic tone all increase ICP. The use of adequate sedation and analgesia with agents such as propofol and fentanyl is helpful with these issues, with propofol being the first-line agent.

CSF drainage: One of the major benefits to ICP monitoring with an intraventricular catheter (or extraventricular drain EVD) is that it allows for CSF diversion. Unclamping the intraventricular catheter and draining 3–5 mL of CSF is one of the fastest and most effective methods of lowering ICP.

Osmotherapy: Mannitol is a commonly used ICP-reducing osmotic agent in the setting of TBI. It is an osmotic diuretic that lowers ICP through both rheologic and osmotic effects. Mannitol administration initially expands plasma volume reducing blood viscosity, increasing CBF, and increasing cerebral oxygen delivery. More delayed osmotic effects dehydrate the intracellular and interstitial brain compartments pulling water intravascularly, thus resulting in a net diuretic effect, which may not be desirable in hypotensive patients. Furthermore, a rebound effect of ICP elevation has been described.^{40,41} Bolus administration at doses of 0.25–1 g/kg is effective.¹¹ In an effort to prevent renal toxicity, a cutoff serum osmolality of 320 mOsm is often used; however, in the setting of ICP crisis, a higher osmolality may be tolerated. Acute renal toxicity is well described with mannitol use.⁴⁰

Hypertonic saline is also an osmotic agent that effectively lowers ICP. Hypertonic saline concentrations from 1.5% up to 23.4% are frequently used in clinical practice, and it may represent an important alternative to mannitol for controlling ICP.⁴² It is often preferred in patients with hemodynamic instability or patients requiring sustained volume expansion. Avoiding severe hyponatremia ($Na > 160$ mEq/L) is also prudent as this has been associated with increased mortality.⁴³ Regardless of osmotic agent, maintaining euvolemia is crucial to TBI care.

SECOND-LINE THERAPIES

Hyperventilation: Hyperventilation reduces ICP by causing cerebral vasoconstriction and thus reducing intracranial blood volume, but the vasoconstriction also significantly reduces cerebral blood flow. The only randomized controlled trial addressing this question found significantly worse outcomes at 6 months in a subgroup of patients hyperventilated to a $Paco_2$ of 25 mm Hg as compared with the control group ventilated to a $Paco_2$ of 35 mm Hg.⁴⁴ Prophylactic hyperventilation is not recommended in TBI patients.¹¹ We recommend continuous $ETCO_2$ monitoring and correlation to serial arterial blood gas measurements for control of $Paco_2$.

However, hyperventilation may be briefly used as a temporizing measure in an acute setting such as active or imminent herniation. The clinical response is very fast and lasts anywhere from a few minutes to hours. When employed, $S_{jv}O_2$ or $P_{bt}O_2$ monitoring is recommended.¹¹

Surgical decompression: Approximately 10–15% of severe TBI patients experience intracranial hypertension refractory to maximal medical therapy.⁴⁵ Surgical decompression is frequently indicated in patients receiving evacuation of hematoma,²⁶ but indications for bilateral decompressive craniectomy for diffuse injury without mass lesion is unclear.²⁹ Certainly, it helps to lower ICP, but mortality may not be affected. Decompressive craniectomy should be considered for patients refractory to medical therapy.

Barbiturate therapy: TBI patients with intracranial hypertension refractory to maximal medical and surgical therapy may be treated with high-dose barbiturates.¹¹ The beneficial effects of barbiturates are attributed to their ability to induce cerebral vasoconstriction, decrease cerebral metabolism and CBF, and act as a free radical scavenger. However, routine or

 **TABLE 35-4: Treatment of ICP and CPP in Severe TBI**

Initial Interventions	First-line Therapies	Second-line Therapies
Elevation of HOB with good head and neck alignment	Adequate sedation and analgesia	Short-term hyperventilation
Maintain normothermia	CSF drainage	Decompressive craniectomy
Keep PaO ₂ > 70 mm Hg or SpO ₂ > 94%	Osmotherapy with mannitol or hypertonic saline	Barbiturate therapy
Tight control Paco ₂ to 35 mm Hg		Hypothermia
		Decompressive laparotomy

prophylactic administration of barbiturates for severe TBI is not indicated due to the common adverse side effect of hypotension, which likely offsets any CPP improvement from ICP lowering by also lowering MAP.¹¹

If barbiturate coma is to be used as a second-tier agent, pentobarbital may be administered with an intravenous loading dose of 10 mg/kg over 30 minutes followed by an infusion at 1–3 mg/kg/h titrated to burst suppression on EEG.¹¹ Barbiturates are myocardial depressants, and thus aggressive hemodynamic support (usually with vasopressors) is necessary to maintain systemic blood pressure.

Hypothermia: Certainly hypothermia has been shown to improve outcomes in anoxic brain injury due to cardiac arrest,^{46,47} but its use as a prophylactic measure in patients with severe TBI is unclear. Current literature and subsequent guidelines do not support its widespread use, although there was some trend (although not statistically significant) toward improved outcomes.¹¹

Nonetheless, hypothermia should be considered in patients with refractory high ICP. The decreased metabolic demand from hypothermia may decrease inflammation, edema, and cell death. A target temperature between 32°C and 35°C has been used in neurotrauma patients previously, and hypothermia should be induced for at least 48 hours with slow rewarming and monitoring for associated side effects.¹¹

With the recent publication using 36°C in cardiac arrest,⁴⁸ more aggressive fever prevention (or controlled normothermia)

may have a role instead of hypothermia, but has yet to be adequately studied.

Decompressive laparotomy: Multiple cases of decompressive laparotomy for refractory high ICPs have been reported with fairly effective results.^{49,50} Even though abdominal compartment syndrome was not diagnosed in these patients, approximately two-thirds benefitted with sustained decreases in ICP and increased survival. It is currently unclear which patients may benefit from decompressive laparotomy, but decompression should be considered in patients with elevated intra-abdominal pressures and elevated ICP that is refractory to other therapies.⁵¹

Steroids

Corticosteroids have no role in the management of severe TBI. Class I data from large randomized controlled studies indicate that they neither improve outcome nor lower ICP in this setting.^{11,52} Indeed, the data suggest that the use of steroids is harmful in TBI patients.

Seizure Prophylaxis

Seizures may be seen in up to 25% of TBI patients within the first 7 days of injury and in up to 42% after this.¹¹ The literature currently supports the use of seizure prophylaxis to decrease the occurrence of early (within 7 days of injury) post-traumatic seizures (PTS) but not for late PTS. Therefore, continuation of anticonvulsant therapy for more than 1 week following TBI is not recommended if seizures do not occur during the first week after TBI.¹¹

While phenytoin has been the historical drug of choice in the setting of TBI, use of levetiracetam may be similarly beneficial with a better side-effect profile, fewer significant drug–drug interactions, and no need for serum level monitoring.^{53,54}

 **TABLE 35-5: Changes in Neurologic Status**

Change in Neurologic Status	Testing/Evaluation to Consider
Intracranial event	Head CT
Seizure	EEG
Vasospasm	CT angiography or transcranial Doppler
Hypoxia or hypo/hypercarbia	Arterial blood gas (ABG)
Hypoglycemia or electrolyte abnormality	Fingerstick glucose and/or basic metabolic panel with serum osmolality
Medication effect or medication/drug withdrawal	Clinical diagnosis
Hypotension or fever	Standard ICU hemodynamic monitoring

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Spinal Cord Injury

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INTRODUCTION

Traumatic spinal cord injury (TSI) represents pathologies that result from a diverse spectrum of primary insults to the central nervous system (CNS). The incidence of TSI is about 12,000 cases annually in the United States and often affects young, otherwise healthy individuals.^{1,2} In addition to the long-term physical disabilities and the psychosocial impairments seen in neurotrauma survivors, the economic burden of TSI is significant. The United States currently spends \$5.6 billion annually on the treatment of spinal cord injuries. It is estimated that the lifetime total cost directly attributable to spinal cord injury in a 25-year-old patient may exceed \$3 million.¹

Advancements in our understanding of the pathophysiology of CNS injury post-trauma have led to improvements in the critical care of patients with TSI. For spinal cord-injured patients, it is crucial that a multidisciplinary approach be taken from the outset. Similar to the management of traumatic brain injury (TBI) patients, the foremost principle guiding the management of TSI patients is to minimize the secondary neural injury that inevitably follows a primary CNS insult. Appropriate and timely emergency stabilization, critical care management, and surgical interventions are essential for delaying the progression of secondary CNS injury. Toward this end, the clinician treating TSI patients must be able to assess, monitor, and treat the multitude of physiologic derangements that result from and also facilitate CNS injury.

In this chapter, we review the epidemiology, pathophysiology, and critical care management of TSI patients. Because neurosurgical intervention—whether at the bedside or in the operating room—is often necessary for TSI patients, the surgical indications for pathology encountered in the emergency and critical care setting will also be reviewed.

EPIDEMIOLOGY

The National Spinal Cord Injury Statistical Center (NSCISC) collects and dispenses the most comprehensive epidemiologic data on spinal cord injury in the United States. They estimate the annual incidence of spinal cord injury at 40 cases per million population, representing about 12,000 new cases each year in the United States.^{1,3} About 80% of these injuries occur in males. The most common causes of spinal cord injury include motor vehicle accident in 41.3%, fall in 27.3%, and violence in 15%. Cervical spinal cord injuries are the most common comprising over 50% of lesions within the NSCISC database, followed by thoracic, lumbar, and sacral lesions. Among all levels of injury, cervical lesions confer the worst prognosis, with ventilator dependency having a strong negative association with morbidity and mortality. Death in spinal cord-injured patients most commonly results from respiratory infections and septicemia associated with urinary infections and decubitus ulcers. Despite medical advancements, life expectancies for SCI patients have not improved since the 1980s.^{1,3}

PATHOPHYSIOLOGY

An appreciation for the pathophysiologic mechanisms at work after TSI is important for the development and implementation of effective clinical therapeutic strategies. The injury due to TSI can be understood in terms of primary and secondary insults to neural tissue. Primary injury denotes the initial mechanical damage secondary to energy transmission during impact, whereas secondary injury results from the destructive tissue-intrinsic and body systemic response to primary injury. There have been no medical advancements that have been able to repair damage done to the CNS from a primary insult. Therefore the critical care of TSI patients is directed at minimizing secondary injury. Detailed accounts of the molecular and cellular mechanisms of TSI have been given.⁴⁻⁷ Here, we present a concise review of the pathophysiology of TSI with emphasis on delineating pathologic processes that are routinely targeted clinically.

Blood Flow

TSI is associated with focal and/or global hypoperfusion to the spinal cord.^{5,8,9} Hypoperfusion can result from a number of mechanisms including microvascular or macrovascular damage, vasospasm, neurogenic/spinal shock, loss of autoregulation, or mechanical tissue disruption. Decreased blood flow to neural tissue results in ischemia and, ultimately, infarction as cellular metabolic demands exhaust available resources. Many studies of animal models have been able to show an inverse relationship between the duration of ischemia and recovery.^{3,10-14} The evidence suggests this may be true in human TSI patients as well; however, further studies are warranted.^{15,16}

Paradoxically, focally increased blood flow resulting in hyperemia may also result from acute injury to neural tissue. Hyperemia is similarly as deleterious to the injured spinal cord as hypoperfusion. Mechanistically, both processes result in a mismatch between blood flow and cellular metabolism. Additionally, by facilitating oxidative damage to cells and promoting tissue edema, hyperemia further promotes secondary injury in the acute setting.^{4,5}

Metabolism

Metabolic dysfunction results after TSI due to impaired delivery and/or utilization of oxygen and glucose within the injured spinal cord.^{4,5} Because neural cells depend on the production of high-energy molecules from aerobic metabolism to meet their energy requirements, even modest reductions in oxygen and glucose are poorly tolerated.⁴ The ionic fluxes associated with primary cellular injury result in the initiation of energy-dependent processes such as membrane transport in an attempt to restore homeostasis. As energy stores become depleted, especially within the ischemic penumbra, cell death occurs.⁴

Inflammation

The robust inflammatory reaction seen within the damaged spinal cord is a major component of both negative secondary

injury processes and positive, reparative processes.^{4,5} At the site of injury, leukocyte recruitment and concurrent expression of inflammatory mediators such as tumor necrosis factor (TNF)- α , interleukins, and complement molecules promote vascular permeability, edema, and progressive tissue damage. Inhibition of this cytotoxic inflammatory milieu is a major target for the development of neuroprotective therapies.

Excitotoxicity

TSI is associated with excessive release of excitatory neurotransmitters such as glutamate in response to hypoxia.^{4,5} This, in turn, results in major ionic flux involving sodium, potassium, and calcium across cell membranes. The accumulation of intracellular calcium in particular is associated with many toxic processes such as lipase and peroxidase activation as well as free radical generation.

ETIOLOGIES OF INJURY

Traumatic spinal cord injuries are primarily injuries of blunt force trauma, with motor vehicle accidents and falls being the most common sources of injuries. The complex force vectors of blunt trauma can lead to very varied injury patterns, but some injuries are directly related to more specific forces during the trauma. Injuries caused by flexion include wedge fractures of the anterior body, teardrop fractures, clay shoveler's fractures, subluxations, bilateral facet dislocations, atlanto-occipital dislocations, and axial dislocations. Extension injuries include hangman's fracture and extension teardrop fractures, while compression injuries include burst fractures and Jefferson fractures.

INITIAL ASSESSMENT AND CLASSIFICATION

The initial assessment of all neuro-trauma patients should begin with the familiar ABCs: evaluate the airway, confirm breathing with effective ventilation, and assess the circulatory status. Clinically deteriorating patients and those with a Glasgow Coma Scale (GCS) score of ≤ 8 should be intubated because they are unable to adequately protect their airway. Newer studies have looked at whether this should be attempted in the field by EMS or whether patients can be simply ventilated with bag-valve mask in order to expedite their arrival to a trauma center.¹⁵⁻¹⁸ These studies suggest that, even with a decreased level of consciousness, patients who can be easily ventilated with a mask may benefit from being oxygenated solely via bag-valve mask during their transport. The patients were then reassessed upon arrival to a trauma center where intubation could be quickly performed in a more controlled environment.¹⁵⁻¹⁸ Other studies have looked at the devices used to intubate patients and have compared the video laryngoscope or glidescope to direct laryngoscopy.^{13,14} Most studies have been able to show that there is less cervical movement and a higher rate of success using video laryngoscopy; however, there is at least one study suggesting that use

of the glidescope in trauma patients led to more desaturations during intubations.^{17–18} More research is needed in this area to determine an optimal plan for how and when to intubate these patients to help ensure the best outcome.

Precautions such as logrolling and inline stabilization during intubation are prudent until spinal stability is verified.^{19–24} In the past, cervical hard collar placement and body immobilization on a rigid backboard was recommended for all trauma patients.²⁰ Newer guidelines state that patients without any alterations in consciousness, distracting injury, and without midline neck pain or neurologic deficits should not be routinely boarded and collared.²¹ These decisions will ultimately be left to the EMS providers during initial transport. Ensuring proper education and training of the EMS team is essential so that patients suspected of spinal cord injury are properly treated and expedited to the nearest trauma centers.

Cardiac, hemodynamic, respiratory, and pulse oximetry monitoring is necessary for all patients with TSI.^{16,17} Hypoxemia ($\text{SaO}_2 < 90\%$) and hypotension (systolic blood pressure < 90 mm Hg) should be avoided in TSI patients because the available evidence suggests that, like traumatic brain injury patients, outcomes have been shown to be worse if hypoxia or hypotension is present.^{16,17,24} TSI patients must be continually monitored for changes in their ability to maintain ventilation, oxygenation, and perfusion. As their injury evolves, their ability to compensate is often lost. Intubation, volume resuscitation with intravenous fluids or transfusion, and the use of vasopressor medications may be necessary to achieve these initial goals, especially for patients experiencing neurogenic shock.

After the patient has been stabilized and the ABCs have been addressed, visual inspection of the general physical condition of the patient should be carried out. Evidence of basal skull fracture (periorbital or postauricular ecchymoses, cerebrospinal fluid [CSF] rhinorrhea/otorrhea), facial fracture, or spine deformity should be noted. As previously stated, these are complex patients who may often have to be intubated for various reasons. It is important that at least a basic neurologic exam is conducted as early as safely possible. If the patient has not arrived to the trauma bay intubated, a quick neurologic exam should be considered before the patient is sedated or paralyzed. At a minimum, the initial neurologic examination should encompass assessment of the following: (1) level of consciousness with a determination of the GCS (Table 36-1); (2) cranial nerve (CN) function with particular attention to the size, symmetry, and reactivity of pupils; and

(3) gross motor and sensory examination of the extremities. A more detailed motor exam and determination of a specific sensory level is appropriate once the patient has been stabilized. Additionally, a digital rectal exam checking for voluntary anal sphincter contraction should be performed, and an American Spinal Injury Association (ASIA) impairment scale grade (see below) should be assigned.^{25–30}

It is generally accepted that, while in the acute period, patients with TSI should be neurologically examined on a regular basis, which has been defined as at least every hour for the first 24 hours (hyperacute period) and then less often as clinically indicated. In a patient with only a spinal cord injury, this neurologic testing can be easily accomplished and does not seem to otherwise interrupt therapy. However, many spinal cord-injured patients have a more complex traumatic picture that often includes traumatic brain injury. In these patients, a disruption of sedation needed to perform these detailed exams may lead to frequent increases in intracranial pressure. As we have begun to examine the importance of timing of surgical interventions for spinal cord injury, it will become increasingly important in the multitrauma patient to understand how often these exams change management and if an hourly re-exam is necessary for optimal treatment.

RADIOGRAPHIC EVALUATION

In patients with evidence of spinal cord injury, a computed tomography (CT) scan of the entire spine should be performed to evaluate known spinal lesions and to rule out additional, noncontiguous vertebral injuries.²⁷ These patients should also be considered for additional imaging based on physical findings and clinical suspicion, bearing in mind that spine injuries may lead to less reliable physical exam findings. Once the patient has been stabilized for transport, a magnetic resonance image (MRI) of the known or suspected area of spinal cord injury should also be performed. MRI is superior to CT for the detection of traumatic intervertebral disc herniation, spinal ligament disruption, and epidural hematoma (EDH).

Cervical Spine Clearance

Cervical spine injury is found in association with TBI in 2–6% of patients. Thus, cervical spine immobilization with a hard collar should be continued in all trauma patients until either clinical or radiographic clearance can be accomplished.^{31–38} Using either Nexus criteria or Canadian C-spine rules it is



TABLE 36-1: Glasgow Coma Scale

Points	Eye Opening	Verbal Response	Motor Response
6	—	—	Obeys commands
5	—	Oriented	Localizes to pain
4	Spontaneous	Confused	Withdraws to pain
3	To speech	Inappropriate	Flexor posturing
2	To pain	Incomprehensible	Extensor posturing
1	None	None	None

possible to clinically clear some trauma patients. For all other patients, including obtunded or intoxicated patients and awake symptomatic patients, initial imaging should include cervical spine CT scan. Radiographs in three views (anteroposterior [AP], lateral, odontoid) with clear visualization from the craniocervical junction to the C7–T1 junction used to be acceptable for cervical spine clearance, but newer evidence suggests that all patients in need of cervical spine clearance should receive a CT. If CT is unrevealing and patients continue to have midline tenderness or deficits, either dynamic flexion–extension x-ray or cervical spine MRI is required for clearance. There are some newer studies that show that, without a neurologic deficit, CT alone may be enough to provide cervical spine clearance. This will continue to be an interesting area of study until more specific recommendations concerning CT and cervical spine clearance can be made.^{39–55}

Spinal Cord Injury Syndromes

Spinal cord injuries may be categorized as either complete or incomplete (Table 36-2). Both categories of acute spinal cord injury require patients to be monitored and treated in a critical care setting.^{20–22}

A complete spinal cord injury (ASIA A) results in loss of all motor and sensory function at or just caudal to the cord lesion level. Acutely, spinal shock with flaccid paralysis, areflexia, and autonomic dysfunction is seen below the lesion level.^{34,35} For cervical lesions, this may result in bradyarrhythmias, conduction block, and hypotension due to disrupted sympathetic outflow. This is known as *neurogenic shock*. Although this clinical picture represents a spinal cord transection syndrome, an actual anatomic transection is rare.³⁴

In contrast to complete injury, incomplete spinal cord injuries (ASIA B–D) are associated with varying levels of motor and sensory preservation. Several spinal cord injury syndromes have been described and include the following:

- *Central cord syndrome*: This syndrome presents with upper greater than lower extremity weakness, urinary dysfunction, and varying degrees of sensory disturbance. It is thought to result from a cervical hyperextension injury in the setting of cervical spondylosis.

- *Brown-Séquard syndrome*: Penetrating trauma resulting in spinal cord hemisection is the usual cause of this syndrome. The clinical findings of Brown-Séquard syndrome include (1) ipsilateral motor paralysis and loss of posterior column function (proprioception and vibratory sense) below the lesion and (2) contralateral dissociated sensory loss with loss of pain and temperature but preserved light touch sensation.
- *Anterior cord syndrome*: Cord infarction in the territory of the anterior spinal artery causes this syndrome. Traumatic etiologies such as disc herniation or retropulsion of a vertebral body fragment may result in occlusion of the anterior spinal artery causing paralysis below the lesion level and bilateral dissociated sensory loss (pain and temperature sensation) with sparing of position sense.
- *Conus medullaris syndrome*: This syndrome affects the most caudal region of the spinal cord and presents with bladder and anal sphincter dysfunction, impotence, and saddle anesthesia. Lower extremity motor weakness may be limited. Conus medullaris syndrome must be distinguished from cauda equina syndrome, which affects lumbosacral nerve roots rather than the spinal cord. Pain and lower extremity weakness are more prominent in cauda equina syndrome.
- *Posterior cord syndrome*: This syndrome is poorly defined and uncommonly seen in TSI. Lesions causing this syndrome damage the dorsal columns, causing reduced proprioception, paresthesias, and dysesthetic (burning) pain. Alternate descriptions include additional corticospinal tract involvement producing weakness below the lesion.

SURGICAL INDICATIONS

The initial management of TSI patients aims to both stabilize and identify pathology requiring emergent surgical intervention. A working knowledge of the surgical indications for the most commonly seen neurosurgical pathology in this population is therefore essential for any physician caring for TSI patients.

The indications for emergency surgery in TSI patients are very specific to each type of injury. Some injuries may respond well to immobilization while other injuries require expedient decompression and surgical stabilization.^{56–64} Cervical injuries that tend to require only immobilization include occipital condyle fractures, stable C1 fractures, type 1 and type 3 dens fractures, spinous process fractures, isolated wedge fractures, and extension teardrop fractures.^{63,64} Compression fractures generally respond well to immobilization unless compression is > 25%, there is retropulsion of bony fragments, or there are neurologic deficits.^{63,64} In these cases, surgical intervention is usually necessary.

Decisions about if and when to operate are very complex in these patients. These patients often have multiple injuries, which makes surgical planning only more complicated. Early involvement of neurosurgical specialists is essential as clinical judgment of experienced practitioners must guide management in each unique scenario.



TABLE 36-2: American Spinal Injury Association (ASIA) Impairment Scale

Grade	Features
A	Complete injury. No motor or sensory function below lesion level
B	Incomplete injury. Sensory but not motor function preserved below lesion level
C	Incomplete injury. Muscle grade less than 3 in more than half of key muscles below lesion level
D	Incomplete injury. Muscle grade 3 or more in more than half of key muscles below lesion level
E	Normal function

Spinal Decompression and Stabilization

The indications for emergency decompression and stabilization in TSI patients are still being defined.^{56,57} The Association of Neurological Surgeons has put together a joint committee to continually review the literature and begin to better clarify specific indications. Several animal studies suggest that early decompression is beneficial, but the available human studies do not consistently indicate improved neurologic outcomes. A recent systematic review concluded that urgent decompression in patients experiencing neurologic deterioration, with bilateral locked facets in the setting of incomplete tetraplegia, or cervical cord injury may be appropriate.⁵⁸ Further studies and continued review of the literature are warranted to clarify the role of emergent surgical intervention in TSI patients.

INTENSIVE CARE MEASURES

No discrete segregation exists between the emergency care, the surgical care, and the critical care of neurotrauma patients. The intensive care management of TSI patients begins in the field with first responders and continues until the patient is stable for intensive care unit (ICU) discharge. At all phases of care, the goal is to prevent additional primary injuries and to minimize the extent of secondary injury to the CNS. The recommendations set forth in the American Association of Neurological Surgeons/Congress of Neurological Surgeons Joint Section on Disorders of the Spine and Peripheral Nerves' *Guidelines for the Management of Acute Cervical Spine and Spinal Cord Injuries*^{63,64} are invaluable resources detailing medical management. Additional guidelines have been released in an attempt to optimize prehospital, combat-related, and neurosurgical care.

Blood Pressure and Oxygenation

As already emphasized in the section "Initial Assessment and Classification," both hypotension (systolic blood pressure < 90 mm Hg) and hypoxia (SaO_2 < 90% or PaO_2 < 60 mm Hg) should be avoided.^{8,21–23} As an additional measure to improve spinal cord perfusion in TSI patients, it is recommended that a mean arterial pressure (MAP) of > 85 mm Hg be maintained for 7 days after the injury.^{8,21–23} At a minimum, arterial and central venous pressure (CVP) line placement is usually done in neurotrauma patients. Arterial catheter device monitors, Swan-Ganz catheter placement, and serial echocardiogram assessments may also be helpful for hemodynamic optimization.

Hypothermia

Systemic hypothermia with target temperatures between 33°C and 35°C have been used in neurotrauma patients. In the TSI population, the evidence for therapeutic benefit from systemic hypothermia seems promising, but more prospective studies are needed. A committee from the Joint Section of the AANS and the CNS concluded that there is insufficient

evidence to recommend either for or against the practice of local or systemic hypothermia in the treatment of acute spinal cord injury.^{65,66}

Steroids

Previously findings from the second National Acute Spinal Cord Injury Study (NASCIS II) formed much of the basis for using corticosteroids after TSI.^{66–68} More recently, multiple studies have shown that steroids do not ultimately improve neurologic recovery and may have harmful side effects.^{69–72} There is no class 1 or 2 evidence that shows that steroids are effective, and the FDA does not approve of steroids for the treatment of spinal cord injury. The recommendations in all the recent guidelines are that steroids do not have a role in the treatment of spinal cord injury.

Other Therapies

Other pharmacologic agents and therapies have been researched in the search for an effective neuroprotective agent in spinal cord injury.^{73,74} This research is ongoing but has yet to offer any advancements in the treatment of spinal cord injury. More recently, a procedure involving transplantation of olfactory cells and Schwann cells has shown some promising results in a few cases, but more research is needed.^{73,74}

CONCLUSIONS

Traumatic spinal cord injury is a prevalent life-altering disease. Currently, minimizing secondary injuries is the best therapy that can be provided to maximize neurologic function and recovery of the injured. This requires a consistent cooperative practice involving prehospital staff, emergency medicine personnel, intensive care teams, neurosurgeons, and rehabilitation and social service workers. There will need to be continued research directed at improving therapies as well as innovating newer ways to provide neuroprotection or regeneration.

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Brain Death

Jacob S. Towns • Nash Whitaker • Timothy J. Ellender

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INTRODUCTION

Brain death is defined as the complete and irreversible loss of both cerebral cortical function and involuntary activity (brainstem function) necessary to sustain life.¹ The concept of “death” can be nebulous because it contains biological, moral, and legal/political connotations. Brain death, although defined inconsistently, is used as an indicator of legal death by many authorities.^{1–8} Clinically, injury and illness may irreversibly injure various parts of the brain causing neuronal death while other parts of the brain may remain alive; thus, historically, the term “brain death” has been used (sometimes incorrectly) to refer to various combinations of dysfunction.^{9–11} Brain death is not the same as persistent vegetative state, in which the person retains involuntary activity necessary for life and is therefore “alive.” To provide clarity, a President’s Commission study on brain death drafted the Uniform Determination of Death Act (UDDA) in 1980, which was approved by both the American Medical Association (AMA) and the American Bar Association (ABA).^{12–14} The UDDA outlines two ways of determining death: the first is “irreversible cessation of circulatory and respiratory functions,” and the second is brain death.¹³ The UDDA is grounded upon the philosophy that an organism, as a whole, need not suffer total organ failure to be declared dead; only the organ responsible for integration of the whole system needs to have failed.^{2,9,15} This principle is fundamental to our current practice of organ donation and thus allows procurement to occur legally.¹²

The declaration of brain death requires the establishment of the cause of coma, the assessment of reversibility, the elimination of confounding factors, a series of neurologic assessments, and the interpretation of neuroimaging

and confirmatory tests that might be deemed necessary.¹² While expertise in the intricacies of neuropathology might be beyond the scope of emergency medicine, distinguishing brain death from severe brain injury falls within the purview of the practicing emergency physician. The following chapter focuses on the clinical determination of brain death, important pitfalls and mimickers in clinical testing, and presents a review of the most commonly available confirmatory tests.

CLINICAL DETERMINATION

The clinical neurological examination is the cornerstone of the brain death determination (Figure 37-1); however, there is no universally accepted testing algorithm. The specialty of the assessing physician, duration of observation, need for confirmatory testing, and the number of observers and/or exams vary widely internationally.^{5,6,8,12,16} In the United States, typically there is no requirement for a specific declaring specialty, and one physician examination is sufficient for declaration in adults. Alternatively, timing and confirmatory testing tends to vary widely based on state and/or hospital mandate.^{3,8–10}

Before bedside neurological examination can begin for the purpose of brain death declaration, the patient must be evaluated and confounding medical conditions must be ruled out. This includes hypothermia (defined as a core temperature of $\leq 32^{\circ}\text{C}$), hypotension, drug intoxication, neuromuscular blockade, and poisoning, as well as profound electrolyte, acid–base, and endocrine disturbances.^{12,17} Any testing needed to eliminate the possible presence of these conditions should be conducted prior to clinical neurological assessment.

The American Academy of Neurology published practice guidelines for determining brain death in 1995.¹⁸ Three

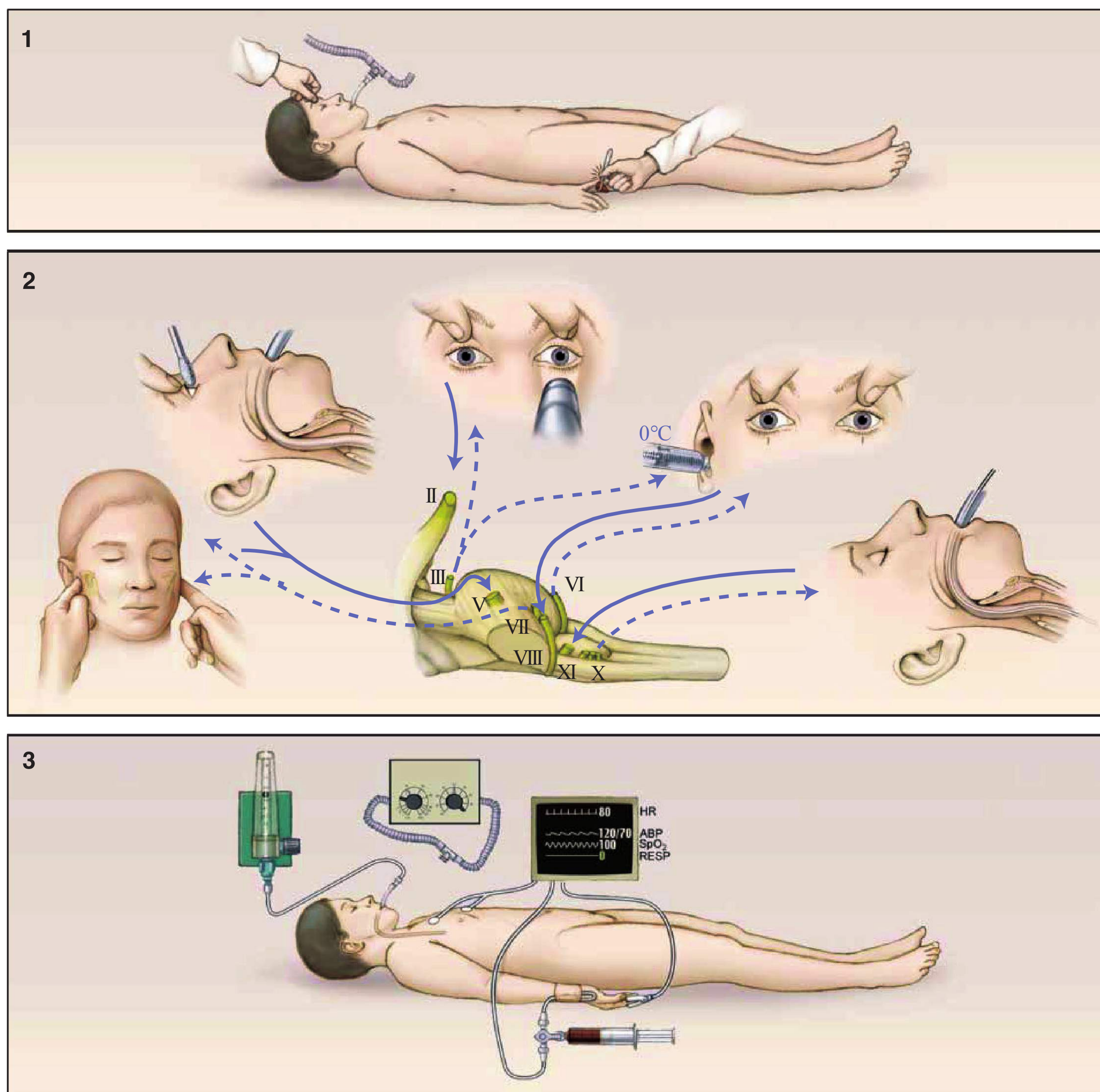


FIGURE 37-1 Clinical examination to assess brain death. Cranial nerves are indicated by Roman numerals; the afferent limbs are represented by solid arrows and the efferent limbs by broken arrows. **Step 1:** Confirm the presence of coma; determine that there is no motor response and the eyes do not open when a painful stimulus is applied to central locations (supraorbital nerve, nail bed, and temporomandibular joint centers). Depicted is the absence of grimacing or eye opening with deep pressure on both condyles at the level of the temporomandibular joint (afferent nerve V and efferent nerve VII). **Step 2:** Clinically assess brainstem reflexes. Depicted is the absence of corneal reflex elicited by touching the edge of the cornea (V and VII), the absence of light reflex (II and III), the absence of oculovestibular response toward the side of the cold stimulus (ice water) (VIII and III and VI), and the absence of cough reflex elicited through the introduction of a suction catheter deep in the trachea (IX and X). **Step 3:** Perform an apnea test. Before beginning, assess: core temperature which should be $\geq 36.5^{\circ}\text{C}$; systolic blood pressure, which should be ≥ 90 mm Hg; and fluid balance, which should be positive for 6 hours. Preoxygenate with 100% Fio_2 for 10 minutes and decrease the ventilation rate in preparation for testing. The ventilator can safely be disconnected if the partial pressure of arterial oxygen reaches ≥ 200 mm Hg and if the partial pressure of arterial carbon dioxide reaches ≥ 40 mm Hg (Pco_2 rises 4 mm Hg the first minute and 3 mm Hg every minute thereafter). Disconnect the ventilator and insert an oxygen catheter to the level of the carina (delivering oxygen at a rate of 6 liters per minute). Observe the chest and abdominal wall for respiration for 8–10 minutes and monitor the patient for changes in vital functions (discontinue testing if respiratory efforts are observed or if the patient becomes hemodynamically unstable). If the partial pressure of arterial carbon dioxide rises to ≥ 60 mm Hg or increases > 20 mm Hg from the normal base-line value, apnea is confirmed.

ABP, arterial blood pressure; Fio_2 , fraction of inspired oxygen; HR, heart rate; Pco_2 , partial pressure of arterial carbon dioxide; RESP, respirations; SpO_2 , oxygen saturation measured by pulse oximetry.

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clinical findings were emphasized to confirm irreversible cessation of all brain functioning: coma (with an identifiable cause), absence of brainstem reflexes, and apnea.^{8,18} As brain death occurs, reflex pathways are eliminated in a rostral-to-caudal direction, with the medulla oblongata being the final component lost.¹² Retained function at the medullary level of the brainstem would result in cough response after tracheal suctioning (brain death exam), tachycardia after the administration of atropine (1 mg), and normal blood pressure.¹² Unfortunately, the medulla can suffer a localized insult resulting in an otherwise intact brainstem and cerebrum. Thus, a meticulous coordination of a stepwise evaluation is necessary to avoid inaccurate diagnosis (Figure 37-2).

Coma

Coma is traditionally assessed using the Glasgow Coma Scale (GCS), rating visual, verbal, and motor responses to stimuli, or the full outline of unresponsiveness (FOUR) score, assessing for eye and motor response, brainstem reflex response, and respiratory patterns.¹⁹ The presence of deep coma can be assessed by the presence or absence of motor responses, including eye opening and movement, to a painful stimulus. Although often tested peripherally to assess motor response in the upper and lower extremities, experts agree that for the purpose of brain death assessment, the painful stimulus should be applied centrally (supraorbital or temporomandibular joint pressure).^{12,20–22} Peripheral stimuli are more likely to result in stimulation of spinal cord reflexes that are not evidence of brain survival, thus confounding the interpretation of a brain death exam.¹²

Brainstem Reflexes

Once coma is established, neurologic testing should assess brainstem reflexes. This exam must be performed in a systematic fashion to avoid errors. The evaluation proceeds through the cranial nerve nuclei as they descend from midbrain to pons to medulla oblongata. The examination does not test for “integrative” properties of the brainstem centers such as the reticular activating system; instead, it focuses on reflex centers adjacent to critical areas and assumes that a loss of reflexes indicates a loss of the adjacent functions as well.^{1,23}

The exam begins with shining a bright light into each eye individually. This tests not only reception in the ophthalmic nerve but also the pupillary response of the oculomotor nerve. The nuclei for cranial nerves (CN) 2 and 3 reside in the midbrain.^{1,15,23} Absence of reflexive constriction bilaterally should be documented to reflect a confirmatory test. The corneal reflex tests the circuit between the afferent fibers of the nasociliary branch of the trigeminal nerve (CN 5) and the efferent fibers of the temporal and zygomatic branches of the facial nerve (CN 7).^{1,23} Both nuclei reside in the pons.^{15,23} This test is elicited by touching the cornea with a piece of cotton or tissue paper. No reflexive eyelid movements should be seen if brainstem function is lost at and above this level of the pons.

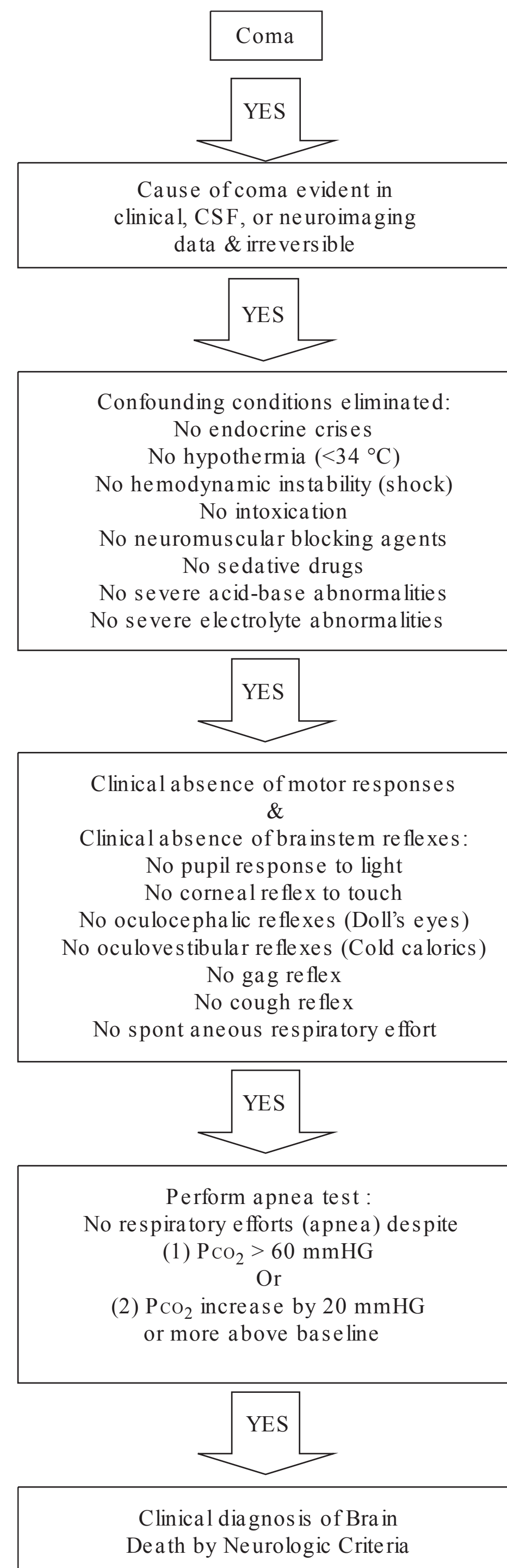


FIGURE 37-2 Algorithm for brain death. C, temperature in Celsius; CSF, cerebrospinal fluid; Pco₂, partial pressure of arterial carbon dioxide.

The oculocephalic reflex, otherwise known as “doll’s eyes,” is assessed next. The cervical spine must be cleared of injury prior to this exam. This reflex encompasses afferent signaling of the vestibulocochlear nerve, CN 8 (nucleus located in the lower pons and the upper medulla) followed

by efferent responses of both the oculomotor (CN 3) and trochlear nerves (CN 4).^{1,23} Both nerves course across the medial longitudinal fasciculus through the midbrain.²³ The test is performed by briskly rotating the head in each direction. If the patient's eyes remain in a fixed position relative to the head such that the patient always appears to gaze in the direction the head is facing, the exam is consistent with brain death. Confirmatory testing should also be performed using cold caloric stimulation of each tympanic membrane (oculovestibular reflex). After patency of the external auditory canal is checked, the head is elevated to 30 degrees relative to horizontal and 50 mL of ice water is used to irrigate each ear canal separately. Movement of the eyes should be absent for 1 minute of observation.¹²

The final brainstem reflexes test the pharyngeal and tracheal responses to stimuli via the gag and cough reflexes, respectively. The pharyngeal reflex arc tests the afferent fibers of the glossopharyngeal nerve (CN 9) and the efferent response of the vagus nerve (CN 10), and both sets of nuclei reside in the medulla.^{1,23} Suctioning of the posterior pharynx should not provoke a gag in a patient who is brain dead. To best test for a cough reflex, a catheter should be inserted through the trachea to the level of the carina with multiple suctioning passes to provoke a response.¹² Lack of response signifies injury to the medulla.¹²

Apnea

The apnea test should be performed only after brainstem reflexes have been confirmed absent. Apnea testing evaluates retained function at the level of the lower medulla.¹² Furthermore, certain prerequisites need to be fulfilled prior to the start of apnea testing. The patient must be normothermic (core body temperature $> 36.5^{\circ}\text{C}$), normotensive (systolic blood pressure > 90 mm Hg), eucapnic (partial pressure of arterial carbon dioxide [Paco_2] 35–45 mm Hg), euvoletic, and normoxic.¹² Preoxygenation with 100% O_2 for either 10 minutes or until Pao_2 is > 200 allows nitrogen washout. This serves two purposes: (1) Nitrogen washout maximizes the negative pressure created by the body's normal $\text{CO}_2:\text{O}_2$ exchange allowing apneic oxygenation and (2) it allows for a large reservoir of oxygen to maximize the length of the apneic period in the setting of rising CO_2 concentrations.¹² Once these parameters have been met, a baseline arterial blood gas should be obtained.

The patient is then disconnected from the ventilator (the sensitivity of modern ventilators precludes them from accurately assessing for the presence of respiratory effort), and passive oxygenation is established by placing an insufflation catheter (often a modified nasal cannula) through the endotracheal tube to the level of the carina. 100% oxygen is delivered at a rate of 6 L/min through this catheter.^{12,24} The patient should be observed closely for any evidence of respiratory movements (chest or abdominal rise or fall). The patient's Paco_2 should be expected to rise at a rate of approximately 3 mm Hg/min.^{12,25} In the absence of respiratory movements, after approximately 8–10 minutes of apnea a repeat arterial

blood gas should be performed.^{12,25} If the Pco_2 has risen to > 60 mm Hg (or > 20 mm Hg over the patient's baseline arterial Pco_2), the apnea test supports the clinical diagnosis of brain death.^{12,24}

MIMICKERS OF BRAIN DEATH

Two of the most important requirements for the diagnosis of brain death are (1) knowledge of the cause of catastrophic brain injury and (2) exclusion of reversible conditions that may mimic brain death.¹⁸ It is worth covering some of the common closely related brain disorders and mimickers of brain death.

Locked-in Syndrome

The locked-in syndrome is a consequence of destruction of the base of the pons resulting in almost complete paralysis. The patient retains consciousness due to an intact reticular formation, retains the ability to voluntarily blink, and retains vertical eye movement.^{7,15} Although this syndrome is not generally reversible, the patient remains very much alive and can interact with his or her surroundings. A very thorough clinical exam is necessary to differentiate this condition from coma and brain death; thus, the significance of a thorough clinical examination cannot be overemphasized.

Coma

Coma is defined as a state of unconsciousness with a complete lack of response to any stimulus, as discussed earlier.¹⁵ Structural causes of coma that would not constitute brain death include localized injury to the reticular formation and/or impairment of both cerebral cortices.²¹ Patients with reversible causes of coma remain “alive”; thus, reversible causes of coma (metabolic, endocrine, and acid–base disturbances) must be excluded as well (Table 37-1).

Persistent Vegetative State (PVS)

Persistent vegetative state is defined as a nonreversible state of bilateral cerebral cortical failure.²¹ It is differentiated from whole brain death by a functioning brainstem with retained control of respiratory and circulatory dynamics despite the patient's inability to meaningfully interact with his or her environment.¹⁵ Despite its irreversible nature, PVS is not universally accepted as a death equivalent and therefore patients with this unfortunate condition do not qualify for the diagnosis of brain death.

Hypothermia

Brain death cannot be determined in the presence of a core body temperature of $< 32^{\circ}\text{C}$.^{12,15} Below 32°C , pupil constriction to light is lost, and below 28°C brainstem reflexes begin to disappear.¹² These changes are not evidence of irreversible injury, thus hypothermia must be excluded as the cause of any deficits.


TABLE 37-1: Common Reversible Causes of Coma or Depressed Consciousness

Etiology	Clinical Examples
Focal	
Structural lesions	Brain abscess
	Brain mass
	Brain stem infarction
	Head trauma (cerebral contusions, epidural or subdural hematoma)
	Hydrocephalus (acute)
	Intraparenchymal hemorrhage
Nonstructural lesions	Subarachnoid hemorrhage
	Seizure
	CNS infection
Global/Diffuse	
Drug	Cerebral edema
	Alcohol
	Antiepileptic agents
	Baclofen
	Cholinergic agents
	Dissociative agents
	Isoniazid
	Opiates
	Psychiatric medications (antipsychotics, serotonin uptake inhibitors, tricyclic antidepressants)
	Sedatives
Endocrine/metabolic	Diabetic ketoacidosis
	Hepatic failure/encephalopathy
	Hypercalcemia
	Hypercapnia
	Hyperglycemia
	Hypernatremia
	Hyperthyroidism (Storm)
	Hypoglycemia
	Hyponatremia
	Hypoxia
	Hypothyroidism
	Uremia
	Wernicke encephalopathy
Infection	Encephalitis
	Meningitis
	Sepsis
Other/environmental	Cerebral edema
	Diffuse axonal injury
	Hypertensive encephalopathy
	Hyperthermia
	Hypothermia
	Neurodegenerative/autoimmune syndromes (Amyotrophic lateral sclerosis [ALS], Guillain-Barré)
	Post arrest anoxia/syndrome
Toxins	Asphyxiants (argon, nitrogen)
	Carbon monoxide
	Inhalants
	Methemoglobinemia
	MDMA

MDMA, methylenedioxymethamphetamine.

Drug Intoxication/Neuromuscular Blockade

Barbiturate overdose is probably the most well-known drug mimicker of brain death, but general anesthesia, alcohol or drug overdose, tricyclic overdose, and baclofen overdose are also common confounders to the clinical brain death exam. Train-of-four testing in combination with electroencephalogram (EEG) can be used to confirm or refute the presence of neuromuscular blocking agents.^{15,17,26} Drug levels can also be obtained for many common adulterants, but if no level is available, experts recommend waiting five times the drug half-life (in the setting of functioning organs of elimination and normothermia) before proceeding with clinical examination for brain death.⁸ Additionally, when a clinical brain death examination is precluded by confounders, confirmatory testing may be the only option available for definitive diagnostics.⁸

Medical Conditions

Several different autoimmune, general, medical and neurodegenerative conditions can present as mimics of deep coma or brain death. Guillain-Barré syndrome, for example, in its extreme form can present as profound coma and present false positives on clinical examination alone. This condition will self-resolve given appropriate supportive care, and an astute clinician should be alert to a history of slowly progressive neuropathy and confirm the diagnosis with testing (lumbar puncture, electromyography). Amyotrophic lateral sclerosis (ALS) can mimic brain death in its extremes as well, although this disease is generally slowly progressive and rarely presents as an acute unknown condition. Seizure, specifically subclinical status epilepticus, is another common cause of profound coma. A keen review of the history of present illness should arouse suspicion to the possibility of seizure activity, and an EEG should easily diagnose its presence.

Brain Death-Associated Reflexes and Automatism

There are many documented spinal cord reflexes (e.g., Babinski sign) or gross spontaneous movements that confound the clinical brain death exam and result in false-negative results.²² Several can occur spontaneously or in response to a stimulus (tactile and/or noxious interactions; e.g., extubation).^{7,22,27,28} Clinicians should be aware of these automatisms, which should not preclude the diagnosis of brain death. The “Lazarus sign” is a reflexive, nonpurposeful movement that mimics the appearance of a patient grasping for the endotracheal tube.^{7,22} When elicited, one or both arms flex at the elbow(s) with hand(s) brought to face then returned to the bed. The “undulating toe sign,” consisting of plantar flexion of the great toe followed by brief plantar flexion of the second through fifth toes, is another nonpurposeful patterned sequence of movements that can mimic motor response to pain.²² Patients might experience central motor responses with shoulder

abduction/elevation and concomitant back arching and intercostal expansion that can mimic respiratory-like movements.²² These do not generate significant tidal volume and should be differentiated from spontaneous respiratory activity. It is important to note that such reflexes usually cease within 72 hours of true clinical brain death, but movements that cast significant doubt (inability to clinically differentiate them as reflexes) will likely result in a delay in diagnosis of brain death in consideration of confirmatory testing.^{7,17,22}

CONFIRMATORY TESTS FOR BRAIN DEATH

Ancillary testing for the diagnosis of brain death remains an area of controversy.^{17,29,30} Although there is no accepted single best test, there are several common options and future possibilities worth noting. There are three situations when ancillary testing might be required. First, many countries in Asia, Europe, Central America, and South America demand proof of “whole-brain death” (brainstem and cerebrum) prior to the declaration of brain death, and thus require ancillary testing to be performed.^{3,5,10,16} Patients with anatomical defects that prevent thorough clinical examination are a second cohort that might require confirmatory testing. Examples of patient conditions in this cohort might include deaf patients or those with damaged auditory structures, blind patients, those with severe facial swelling after trauma, chronic carbon dioxide retainers, and patients with confounding medical conditions such as paralysis, sedative use, or endocrinologic/metabolic derangements that are not easily reversed.¹⁷ The third and last cohort is young children. Children present many challenges to brain death determination, with established mandates for multiple examination and often confirmation.^{31,32}

Available testing can be divided broadly into two categories: (1) those that evaluate central nervous electrical function and (2) those that evaluate intracranial blood flow.^{17,31} Electrical function testing includes EEG, somatosensory evoked potential, and auditory evoked potential. Blood flow studies include cerebral angiography, transcranial Doppler (TCD), computerized tomographic angiography (CTA), nuclear brain scanning, and magnetic resonance angiography (MRA).

Electroencephalography

EEG is a widely available tool for assessing cortical function, but, importantly, it does not assess subcortical structures including the brainstem.^{12,33} Generalized voltage suppression is the key evidence supporting brain death, and there are specific requirements for sensor placement and device settings during the actual brain death examination.¹² EEG is flawed in that cortical signals can be absent despite ongoing brainstem or subcortical activity however.^{12,29} Additionally, activity can be present in patients who are clinically brain dead, and certain reversible conditions such as barbiturate overdose result in EEGs that falsely indicate brain death.²⁹

Evoked Potentials

Evoked potentials are differentiated by the specific receptors used to trigger activity.³¹ Brainstem auditory evoked response (BAER) testing utilizes auditory stimuli and measures five waves of response.¹⁷ Waves 1 and 2 are generated by the auditory nerve and cochlear nuclei, respectively, and are external to the brainstem. Waves 3–5 assess the brainstem and are absent in brain death.¹⁷ Somatosensory evoked potentials (SSEPs) are elicited with median nerve stimulation.³¹ Waves N18–N20 are present with activity in the medulla

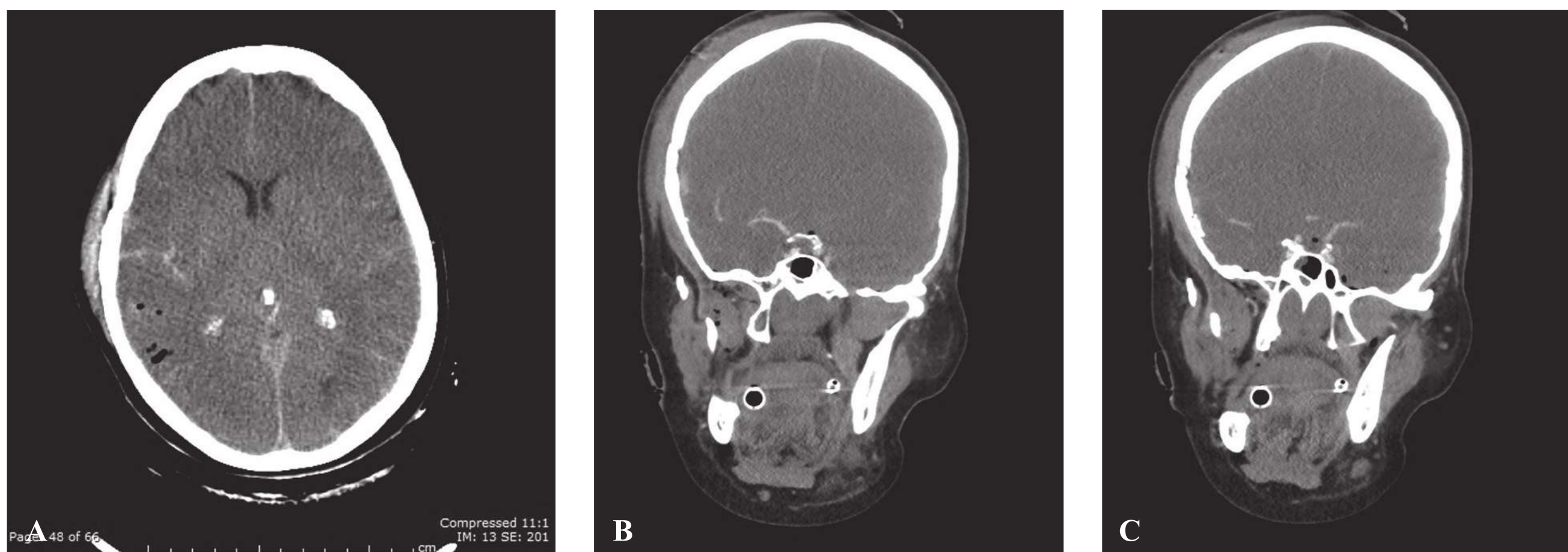


FIGURE 37-3 (A-C). CT head and CT angiography. The patient presented after being struck by a motor vehicle. The CT imaging demonstrates diffuse acute subarachnoid hemorrhage involving the basal and suprasellar cisterns, the sylvian fissures, and multiple sulci.

There is acute subdural hematoma along the interhemispheric fissure and tentorium along with multiple foci of pneumocephalus. The reduced gray–white discrimination is suspicious for anoxic ischemic insult. The patient’s clinical course and exam was consistent with deep coma, but the clinical exam was obscured by massive facial injuries. CTA was obtained to further evaluate blood flow. CTA demonstrates findings consistent with diffuse cerebral edema, increased ICP, and diminished distal branch vessel flow; however, flow was maintained at the level of bilateral carotid arteries and the basilar artery into the Circle of Willis, which did not support “whole brain death.”

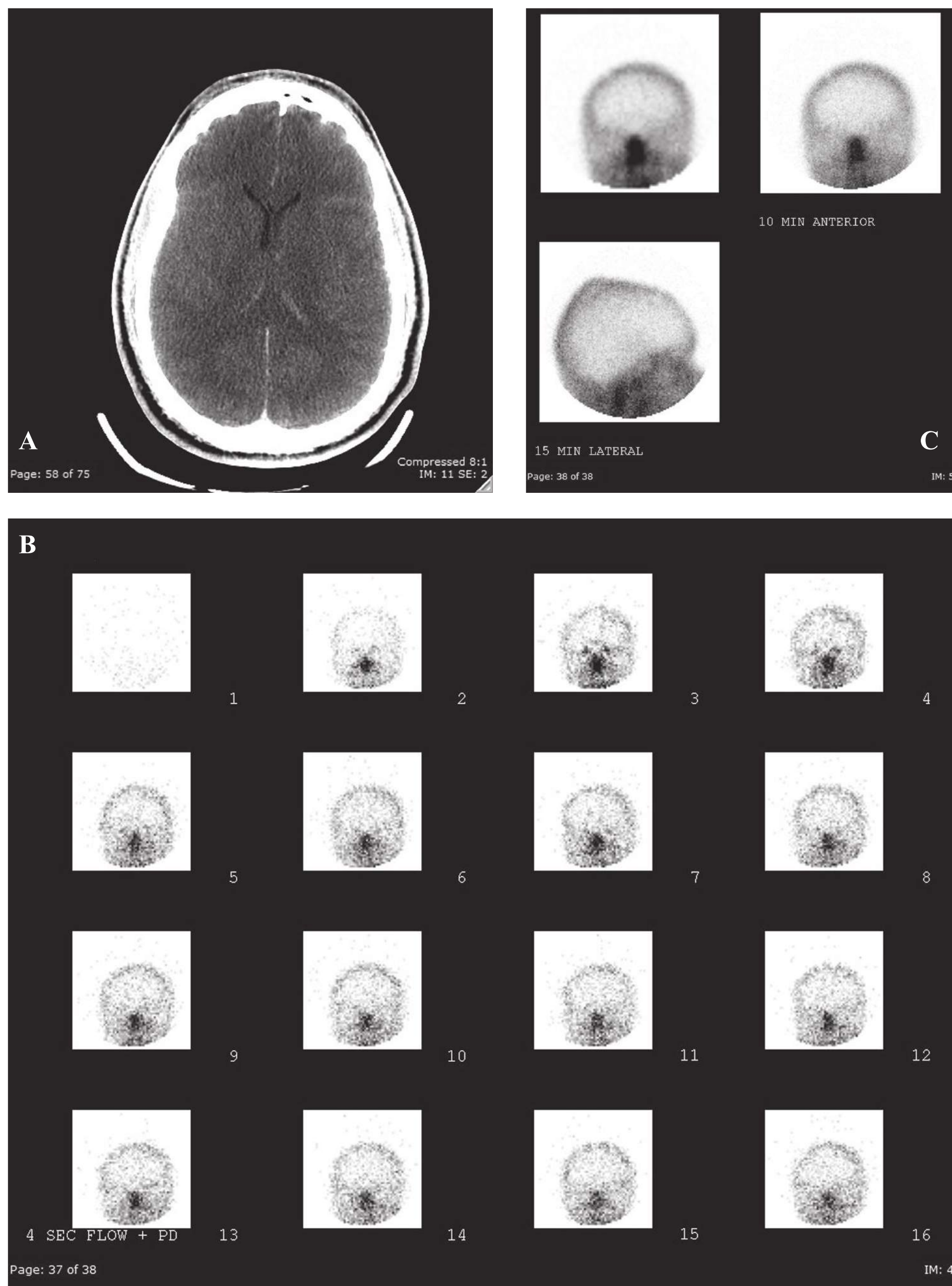


FIGURE 37-4 (A-C) CT head and radionuclide brain flow scan. The patient presented post-motor vehicle collision. The CT imaging demonstrates diffuse subarachnoid hemorrhage, acute intraventricular hemorrhage in the occipital horns, and reduction in gray-white matter differentiation with reduction in lateral ventricle size raising suspicion for increased cerebral edema. Progression in clinical exam was consistent with brain death. Radionuclide Tc-99m HMPAO was administered intravenously and anterior blood (vascular) flow images of the head and neck were obtained followed by a static image of the brain. Gamma camera imaging demonstrates no intracranial blood flow. There is no anterior and middle cerebral arterial blood flow, along with no activity in the cerebral hemispheres, the cerebellar hemispheres, and the brainstem. “Hot nose sign” is present with diversion of blood flow to the external carotid circulation.

through the primary sensory cortex.¹⁷ Wave N9 is generated by the brachial plexus, and N9 absence is one indicator of an invalid test. As with EEG testing, conditions that impact brain electrical activity (sedative drugs, anesthetics, and metabolic derangements) skew test results. Furthermore, localized lesions affecting tested areas can produce results that are consistent with brain death despite ongoing brain activity.¹⁷

Transcranial Doppler

Transcranial Doppler (TCD) is noninvasive, inexpensive, and can be assessed at bedside. A 2 Hz, pulsed-wave probe is used to assess flow in the bilateral middle cerebral and vertebral arteries.³¹ Technical acquisition and timing challenges grossly limit this technology, and, in the setting of complete absence

of flow, brain death cannot be reliably determined with TCD alone. TCD is conclusive only when a reverberating pattern or small systolic peaks with no forward diastolic flow is found in all four vessels tested.¹⁵

Cerebral Angiography (CTA and MRA)

Cerebral angiography studies focus on imaging of bilateral carotid and vertebral arteries and can be considered superior to other confirmatory tests because they are not influenced by CNS depressants or hypothermia.^{17,29} Absent intracerebral filling at the level of the carotid bifurcation or circle of Willis is consistent with brain death.⁸ To be considered confirmatory there must be patent external carotid

circulation and delayed filling of the superior longitudinal sinus.³¹ Any maintenance of flow within the circle of Willis or branch vessels voids confirmation of brain death (Figure 37-3A–C).

Nuclear Brain Scan

Radionuclide scanning relies on the uptake of radioactive tracer into brain parenchyma to evaluate brain perfusion with a gamma camera. Brain-specific or lipophilic tracers that cross the blood–brain barrier (e.g., technetium-Tc-99m hexametazime [HMPAO] or Tc-99m ECD) are preferred over nonspecific or lipophobic tracers (e.g., Tc-99m DTPA), which are considered angiographic radionuclides.³⁴ Tc-99m

Prerequisites (all must be checked)

- ☐ Coma, cause known and irreversible
- ☐ Neuroimaging explains coma.
- ☐ CNS depressant drug effect absent (if indicated toxicology screen; if barbiturates- serum level < 10 µg/mL).
- ☐ No evidence of residual paralytics (electrical stimulation if paralytics used).
- ☐ Absence of severe acid-base, electrolyte, endocrine abnormality.
- ☐ Normothermia or mild hypothermia (core temperature > 36°C).
- ☐ Systolic blood pressure ≥ 100 mmHg.
- ☐ No spontaneous respirations.

Examination (all must be checked)

- ☐ No facial movement to noxious stimuli at supraorbital nerve, temporomandibular joint.
- ☐ Absence of motor response to noxious stimuli in all four limbs (spinally mediated reflexes are permissible).
- ☐ Pupils nonreactive to bright light.
- ☐ Corneal reflex absent.
- ☐ Oculocephalic reflex absent (tested only if cervical spine integrity ensured).
- ☐ Oculovestibular reflex absent.
- ☐ Gag reflex absent.
- ☐ Cough reflex absent to tracheal suctioning.

Apnea testing (all must be checked)

- ☐ Patient is hemodynamically stable.
- ☐ Ventilator adjusted to provide normocarbida (PaCO₂ 35–45 mm Hg).
- ☐ Preoxygenate with 100% FiO₂ for > 10 minutes to a PaO₂ > 200 mm Hg.
- ☐ Confirm patient is well-oxygenated with a PEEP of 5 cm of water.
- ☐ Disconnect ventilator.
- ☐ Provide oxygen via a suction catheter to the level of the carina at 6 L/min or attach T-piece with CPAP at 10 cm H₂O.
- ☐ Spontaneous respirations absent.
- ☐ Arterial blood gas drawn at 8–10 minutes, patient reconnected to ventilator.
- ☐ Pco₂ ≥ 60 mm Hg, or 20 mm Hg rise from normal baseline value.

Apnea confirms Brain Death if ALL above are checked and findings are consistent with exam.

OR:

- ☐ Apnea test aborted.

Ancillary testing (only one needs to be performed or ordered only if clinical examination cannot be fully performed due to patient factors, if apnea testing inconclusive or aborted, or if mandated by law/policy.

- ☐ Cerebral angiogram
- ☐ Radionuclide Tc-99m HMPAO scan
- ☐ EEG
- ☐ TCD

FIGURE 37-5 Brain death checklist. ABP, arterial blood pressure; FiO₂, fraction of inspired oxygen; HR, heart rate; Pco₂, partial pressure of arterial carbon dioxide; RESP, respirations; SpO₂, oxygen saturation measured by pulse oximetry; PEEP, positive end expiratory pressure; CPAP, continuous positive airway pressure; H₂O, water; Tc-99m HMPAO, technetium hexametazime; EEG, electroencephalography; TCD, transcranial Doppler.

HMPAO penetrates brain parenchyma in proportion to localized blood flow allowing measurements of brain perfusion, not just intracerebral circulation.³⁴ Basic protocols call for an injection or angiographic phase followed by a delayed phase obtained minutes after injection. A study that demonstrates absence of intracerebral perfusion shows tracer flowing through the carotid arteries to the skull base where the flow of tracer stops. Presumably, this is due to increased intracranial pressure (Figure 37-4A–C). Lack of radionuclide localization in the middle cerebral arteries, anterior cerebral arteries, and basilar arteries confirms brain death when there is a working clinical diagnosis of brain death.³⁴ Any study showing tracer flow through the carotid arteries to the base of the skull and then into the intracerebral region (the brain) is interpreted as negative for brain death.

SUMMARY

Diagnosing brain death is necessarily a rigorous process. Although in the United States a clinical exam is sufficient to confirm brain death in adults, several foreign countries and a few states regulate who can declare brain death, require multiple exams or delays, and mandate confirmatory studies. Furthermore, some states provide exceptions to the clinical diagnosis of brain death for those with religious exemptions; so, in addition to knowing the specifics of the exam itself, it is also necessary to understand both national and state laws as well as institutional policies regarding brain death declaration.^{1,2} The importance of knowing the laws regarding brain death cannot be understated as this diagnosis marks the transition between brain protective care and organ protective care. Practitioners faced with the possibility of brain death determination may improve compliance with policies through the use of an action checklist and performance scripting (Figure 37-5).

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HEMATOLOGIC AND ENDOCRINE DISORDERS

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Transfusion in Critical Care

Julie A. Mayglothling • Therese M. Duane

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INTRODUCTION

Fresh, warm whole blood most effectively restores red cell mass, plasma volume, clotting factors, and platelets. However, given shortages of blood products, the use of whole blood transfusions is not realistic. The use of component product transfusion is the mainstay of blood banking and transfusion practice, effectively utilizing a scarce resource while matching the components transfused to the specific needs of the patient. Whole blood is usually separated into packed red blood cells (PRBC), fresh frozen plasma (FFP), and platelet concentrate soon after donation. The plasma can be further separated into cryoprecipitate, cryo-poor plasma, or undergo further fractionation to individual plasma proteins.

Indications for blood component therapy can be divided into two main categories: (1) enhancement of oxygen carrying capacity by increasing red blood cell (RBC) mass and (2) replacement of coagulation components due to loss, dysfunction, or consumption.

ANEMIA AND PACKED RED BLOOD CELL TRANSFUSION

Anemia is one of the most common abnormal laboratory findings among critically ill patients. The effect of anemia on outcome and the determination of transfusion triggers has been the subject of much debate in recent literature.

Historically, the decision to transfuse has been guided by the hemoglobin (Hb) concentration, usually 10 mg/dL. However, given the risks associated with PRBC transfusion

and literature supporting better or similar outcomes with lower transfusion triggers, the optimal Hb level at which to transfuse patients remains unclear.

Benefits of RBC Transfusion

The main function of RBCs is to transport oxygen from the lungs to the peripheral tissues. Oxygen delivery (DO_2) is calculated by multiplying the cardiac output (CO) times the arterial oxygen content (CaO_2):

$$DO_2 = CO \times CaO_2,$$

where DO_2 is in mL/min, CO in dL/min, and CaO_2 in mL/dL. And CaO_2 is calculated by the following equation:

$$CaO_2 = (Sao_2 \times 1.34 \times [Hb]) + (0.0031 \times Pao_2),$$

where Sao_2 is the arterial oxygen saturation (in %), 1.34 is the oxygen carrying capacity of hemoglobin in mL/g, [Hb] is the hemoglobin concentration (in g/dL), 0.0031 is the solubility of oxygen in plasma at 37°C, and Pao_2 is measured in mm Hg.

Under normal conditions, DO_2 exceeds oxygen consumption (VO_2) by three to five times. However, in situations where the VO_2 of the peripheral tissues is greatly increased, or DO_2 is decreased by anemia or decreased CO, VO_2 can exceed DO_2 and result in tissue hypoxia. Increasing the [Hb] is one of the ways to increase the blood's oxygen carrying capacity and therefore increase DO_2 . Additionally, transfusion can increase blood volume for patients following acute blood loss or hemorrhage and alleviate symptoms of anemia such as dyspnea, weakness, and fatigue.

Drawbacks of RBC Transfusion

Despite the theoretical benefits of transfusion just described, it is associated with multiple risks. There is risk of human error resulting in a transfusion reaction, most commonly an acute hemolytic reaction, from receiving incorrectly matched blood. Febrile reactions, namely nonhemolytic/noninfectious reactions secondary to antileukocyte antibodies are also possible in up to 7% of blood product recipients. There is risk of allergic reaction ranging from urticaria to frank anaphylaxis that is usually a result of the passive transfer of sensitizing antibodies. Additionally, transmission of communicable diseases such as human immunodeficiency virus (HIV) and viral hepatitis are possible, although this risk, with modern blood banking techniques, is now exceedingly remote.¹ Finally, metabolic derangements can occur with transfusion, such as hypocalcemia and hyperkalemia.

More commonly, especially in the critically ill population, transfusion of PRBCs is associated with increased risk of infection, including wound infections, sepsis, and pneumonia^{2,3}; increased incidence of multiple organ failure⁴; and increased risk of acute lung injury (ALI) and acute respiratory distress syndrome (ARDS).⁵ In addition, transfusions are associated with longer intensive care unit (ICU) and hospital length of stay (LOS), more complications, and increased mortality.⁶ These effects are dose-dependent, meaning that the more units of blood that are transfused, the higher the risk of complications.

The reasons for the increased morbidity and mortality in patients receiving PRBCs is not completely clear, although recent interest has focused on immunomodulating effects of transfused RBCs and RBC storage lesions (age of transfused RBCs) as possible mechanisms. It has been suggested that leukodepleted blood may have less immunomodulating properties and hence reduce the complications associated with the transfusion of nonleukodepleted blood,⁷⁻⁹ but there is still considerable debate about the benefit of leukoreduction and which patients will benefit most from receiving leukoreduced blood.¹⁰ Similarly, age of transfused RBCs has also been suggested as a possible explanation for the adverse effects associated with RBC transfusion. Well-documented changes occur to the RBC product during ex-vivo storage, including a reduction in RBC deformability, altered RBC adhesiveness and aggregability, and a reduction in 2,3-diphosphoglycerate and adenosine triphosphate (ATP). These changes reduce post-transfusion viability of RBCs and limit DO₂.¹¹ The clinical effect of these changes is uncertain; however, some studies have suggested that transfusion of “older” RBCs may be associated with adverse effects.¹²⁻¹⁴ But a 2009 review of 27 studies of postsurgical, ICU, and trauma patients could not establish a definitive relationship between the age of transfused RBCs and outcome in adult patients, except possibly for trauma patients receiving massive transfusion.¹⁵

Transfusion Threshold

There have been multiple retrospective and observational studies that demonstrate that the use of blood transfusions for the

treatment of anemia in hemodynamically stable critically ill patients is not associated with improved outcome. The CRIT Study, performed in the United States and published in 2004, documented that 44% of all patients received blood transfusions and the number of units transfused was independently associated with worse outcomes.¹⁶ Similarly, a European study by Vincent et al. showed an ICU transfusion rate of 37%. In this study, the group of patients who received a transfusion had a higher mortality rate compared to the nontransfused group despite similar degrees of organ dysfunction.¹⁷

The Transfusion Requirements in Critical Care (TRICC) trial conducted in Canada is the only prospective, adequately powered study that randomized patients to either a restrictive transfusion strategy (patients transfused if Hb dropped below 7 g/dL and maintained between 7–9 g/dL) or a liberal strategy (patients transfused when Hb fell below 10 g/dL and maintained at 10–12 g/dL). The overall hospital mortality was significantly lower in the restrictive transfusion group (22.2% vs. 28.1%, $p = 0.05$), and although 30-day mortality was similar in the two groups (18.7% vs. 23.3%, $p = 0.11$), mortality rates were significantly lower in patients randomized to the restrictive transfusion group who were < 55 years of age and less acutely ill. The authors concluded that a restrictive strategy of red cell transfusion is at least as effective as, and possibly superior to, a liberal transfusion threshold for hemodynamically stable critically ill adults.¹⁸ Due to these and other studies, the transfusion threshold for hemodynamically stable critically ill patients has been accepted to be 7g/dL.

There is a subset of patients that may benefit from a slightly higher transfusion threshold, namely those patients with, or at high risk for, myocardial ischemia.¹⁹ The specific threshold for these patients is unclear.

Sepsis

The 2013 Surviving Sepsis Campaign recommends that during the first 6 hours of resuscitation of severe sepsis or septic shock, if tissue hypoperfusion persists despite fluid resuscitation to a central venous oxygen saturation of 70% and a central venous pressure (CVP) of 8–12 mm Hg, then initiation of dobutamine infusion or transfusion of PRBCs to achieve a hematocrit $\geq 30\%$ in attempts to reach the central venous oxygen saturation goal are options.²⁰ This recommendation is based on the Rivers et al. study regarding early goal-directed therapy for sepsis.²¹ Once initial resuscitation of tissue hypoxia is achieved, and in the absence of myocardial ischemia, the restrictive transfusion threshold should then be targeted. Despite this continued recommendation in the 2013 guidelines, this has been tempered slightly relative to the 2008 guidelines based on controversy of the real benefit of red cell transfusion in this situation.

Trauma

The trauma patient with hemorrhagic shock should be transfused regardless of Hb levels. However, in the absence of

ongoing blood loss or hemorrhagic shock, there is no benefit of a “liberal” transfusion threshold in hemodynamically stable trauma patients.²² In a prospective study of more than 15,000 trauma patients, blood transfusion was shown to be an independent predictor of mortality, ICU admission, ICU LOS, and hospital LOS. Those patients who received blood transfusion in the first 24 hours were more than three times as likely to die.²³

Recommendations

A number of guidelines regarding the indications for RBC transfusion have been published between 1997 and 2007. Most recently, a joint task force of the Eastern Association for the Surgery of Trauma (EAST) and the American College of Critical Care Medicine (ACCM) of the Society of Critical Care Medicine (SCCM) performed a comprehensive literature review of the topic and graded the evidence using scientific assessment methods. Table 38-1 includes an abridged summary of their 2009 evidence-based recommendations regarding the use of RBC transfusion in adult trauma and critical care.²⁴

Anemia in critical illness is extremely common, and up to 40% of ICU patients will be transfused during their hospital stay. Physicians must weigh the risks and benefits of transfusion. PRBC transfusions are associated with increased incidence of infection, multiple organ failure, ALI, and ARDS across heterogeneous patient groups. Based on existing literature, no one transfusion trigger should be used in all patients. However, the evidence is sufficient to state that transfusions are rarely beneficial when Hb level exceeds 10 g/dL (HCT > 30%) in the absence of acute blood loss, and using a restrictive strategy for transfusion (transfusing PRBC when Hb levels fall below 7 mg/dL) is just as effective and likely superior to a liberal strategy in hemodynamically stable critically ill patients.

FRESH FROZEN PLASMA

FFP is plasma separated from the RBCs and platelets of whole blood and placed at -18°C or below within 8 hours after collection. By definition, “one unit” of FFP has the equivalent plasma coagulation factors as one unit of whole blood, and one bag contains approximately 200–250 mL. Once thawed,



TABLE 38-1: Abridged Summary of 2009 Clinical Practice Guideline for Red Blood Cell Transfusion in Adult Trauma and Critical Care from the ACCM/SCCM and EAST Practice Management Workgroup²⁶

- A. Indications for RBC Transfusion in the General Critically Ill Patient
 - RBC transfusion is indicated for patients with evidence of hemorrhagic shock. (Level 1)
 - RBC transfusion may be indicated for patients with evidence of acute hemorrhage and hemodynamic instability or inadequate oxygen delivery. (Level 1)
 - A “restrictive” strategy of RBC transfusion (transfuse when Hb < 7 g/dL) is as effective as a “liberal” strategy (transfusion when Hb < 10 g/dL) in critically ill patients with hemodynamically stable anemia, except possibly in patients with acute myocardial ischemia. (Level 1)
 - The use of only Hb level as a “trigger” for transfusion should be avoided. (Level 2)
 - In the absence of acute hemorrhage, RBC transfusion should be given as single units. (Level 2)
 - RBC transfusion should not be considered as an absolute method to improve tissue oxygen consumption in critically ill patients. (Level 2)
- B. RBC Transfusion in Sepsis
 - The transfusion needs for each septic patient must be assessed individually. (Level 2)
- C. RBC Transfusion in Patients at Risk for or with ALI and ARDS
 - All efforts should be initiated to avoid RBC transfusion in patients at risk for ALI and ARDS after completion of resuscitation. (Level 2)
- D. RBC Transfusion in Patients with Neurologic Injury and Diseases
 - There is no benefit of a “liberal” transfusion strategy in patients with moderate-to-severe traumatic brain injury. (Level 2)
- E. RBC Transfusion Risks
 - RBC transfusion is associated with increased nosocomial infection. (Level 2)
 - RBC transfusion is an independent risk factor for MOF and SIRS. (Level 2)
 - There is no definitive evidence that prestorage leukocyte depletion of RBC transfusion reduces complication rates. (Level 2)
 - RBC transfusions are independently associated with longer ICU and hospital LOS, increased complications, and increased mortality. (Level 2)
 - There is a relationship between transfusion and ALI and ARDS. (Level 2)
- F. Alternatives to RBC Transfusion
 - Recombinant human erythropoietin (rHuEpo) administration improves reticulocytosis and hematocrit and may decrease overall transfusion requirements. (Level 2)
 - Hemoglobin-based oxygen carriers (HBOCs) are undergoing investigation for use in critically ill and injured patients but are not yet approved for use in the US. (Level 2)
- G. Strategies to Reduce RBC Transfusion
 - The use of low-volume adult or pediatric blood sampling tubes is associated with a reduction in phlebotomy volumes and a reduction in blood transfusion. (Level 2)
 - Reduction in diagnostic laboratory testing is associated with a reduction in phlebotomy volumes and a reduction in blood transfusion. (Level 2)

FFP must be used within 24 hours or the amount of factors V and III begin to decline. FFP is not a concentrate and must be ABO compatible.

Indications

Transfusion of FFP is indicated in the presence of active bleeding or prior to major invasive procedures with known or suspected coagulation abnormalities due to inadequate production, malfunction, loss, or consumption of multiple clotting factors.^{25–28} Liver failure, warfarin overdose, vitamin K deficiency, and dilutional coagulopathy are some indications for plasma transfusion. Patients with a deficiency of a single clotting factor are more appropriately treated with factor concentrates or cryoprecipitate.

Coagulopathy is supported by prothrombin time (PT) or international normalized ratio (INR) > 1.5 times normal, or activated partial thromboplastin time (aPTT) > 1.5 times the top of the normal range.²⁹ Even in the setting of excessive warfarin effects, transfusion of plasma products should not be used to reverse elevated INR in the absence of bleeding unless urgent invasive or surgical procedures are required.³⁰

Mild to Moderate Coagulopathy

The ability of FFP to reverse mild to moderate coagulopathy (INR 1.1–2) has been shown to be poor.^{31,32} Regardless of the number of units of FFP transfused, there is a low likelihood that the INR will be corrected to normal levels.³³ Specifically, current evidence does not support the use of prophylactic plasma transfusion for minimally invasive procedures in the setting of mildly abnormal coagulation tests such as paracentesis, thoracentesis,²⁶ or central venous catheter insertion.³⁴

Approximately 25% of clotting activity is required for hemostasis. Given that the plasma volume of humans is usually 40 mL/kg, the amount required is approximately 10–15 mL/kg, or 2–3 units of FFP, in the absence of ongoing losses or consumption. This is a general guideline, and clinicians should follow clinical course and coagulation parameters to guide transfusion, remembering that mild to moderate coagulopathy may not be corrected with FFP.

Massive Transfusion

Massive transfusion is generally defined as > 10 units transfused in a 24-hour period. There has been much debate and research dedicated to finding the optimal ratio of PRBCs to FFP and platelets to transfuse in this patient population. Historically, the FFP:PRBC ratio ranged from 1:4 to 1:10, and the initiation of almost any massive transfusion protocol using multiple different ratios had been shown to improve mortality.³⁵ Recent literature in both military and civilian trauma patients supports using higher ratios of FFP. The optimal ratio appears to be between 1:1 and 1:3 FFP to PRBC^{36–38} and is a source of continued study.

CRYOPRECIPITATE

Cryoprecipitate is obtained from the precipitate of frozen plasma once it is thawed. It has high concentrates of factor VIII, fibrinogen, factor XIII, and von Willebrand factor but the volume of cryoprecipitate is smaller, approximately 10 mL, and multiple units are often combined for transfusion. Despite the small volume of cryoprecipitate, it carries the same infectious risk as one unit of FFP. Indications for transfusion of cryoprecipitate include fibrinogen deficiency with levels of < 100 mg/dL, mostly encountered during massive bleeding or consumptive coagulopathy; von Willebrand disease; and hemophilia A when factor VIII concentrates are not available.²⁹

PLATELETS

Platelets are required for primary hemostasis and circulate normally at a count of $150 \times 10^9/\text{L} - 400 \times 10^9/\text{L}$. Each concentrate of platelets contains approximately 5.5×10^{10} platelets and is derived from one unit of whole blood or from plateletpheresis donations. Once collected, platelets can be stored for up to 5 days, and they are pooled with concentrates from multiple donors before transfusion. ABO compatibility is not required but is preferred because small amounts of donor leukocytes and plasma are transfused along with the platelets. Each unit of platelets is expected to increase the platelet count by $5-10 \times 10^9/\text{L}$ in the absence of consumption or ongoing loss, and the usual dose is 1 unit per 10 kg of body weight.

There is no single target platelet count under which transfusion is recommended for all patients. When platelet counts fall below $5 \times 10^9/\text{L}$, there is a possibility of spontaneous hemorrhage and a high risk of hemorrhage with trauma or an invasive procedure.³⁹ Given these risks, platelets should be administered regardless of apparent bleeding when platelets drop below this level.⁴⁰ At counts greater than $50 \times 10^9/\text{L}$, bleeding due to platelet deficiency is unlikely, and prophylactic transfusion is normally not indicated. For patients with active bleeding and those undergoing invasive or surgical procedures, the current recommendation is that platelet counts should be maintained above $50 \times 10^9/\text{L}$.²⁹ Some recommend targets of $100 \times 10^9/\text{L}$ in the setting of intracranial hemorrhage or multisystem trauma.⁴¹

Platelet counts between $5 \times 10^9/\text{L}$ and $50 \times 10^9/\text{L}$ have variable risks of hemorrhage due to thrombocytopenia, and the issue of prophylactic platelet transfusion is controversial between these levels. Clinical observation and evaluation of the patient's other risk factors for bleeding must guide transfusion practices. Prior recommendations were to transfuse platelets whenever the platelet count was less than $20 \times 10^9/\text{L}$, but recent literature recommends lowering that trigger to $10 \times 10^9/\text{L}$.^{42,43}

Patients suffering from a destructive cause for thrombocytopenia rarely benefit from platelet transfusion because the transfused platelets are rapidly destroyed. Patients with such conditions as idiopathic thrombocytopenia purpura (ITP), hypersplenism, disseminated intravascular coagulation

(DIC), sepsis, or platelet antibodies, or those after cardiac surgery with extracorporeal bypass, fall into this category. In the presence of a life-threatening hemorrhage or surgery, transfusion may be beneficial for its short-term effect. Platelet transfusion is contraindicated in such conditions as thrombotic thrombocytopenic purpura (TTP)⁴⁴ and hemolytic uremic syndrome (HUS) because of worse outcomes and is therefore reserved for life-threatening hemorrhage with these conditions. Heparin-induced thrombocytopenia (HIT) was also thought to be a contraindication for platelet transfusion; however, recent guidelines conclude that platelet transfusion can be considered in patients with HIT and overt bleeding or those thought to be at high risk of bleeding.⁴⁵

ERYTHROPOIETIN

The use of recombinant erythropoietin (EPO) has been shown to reduce the need for RBC transfusions in patients with chronic renal failure, as well as in those with anemia of chronic disease, such as cancer and acquired immune deficiency syndrome (AIDS).⁴⁶ Despite the decrease in production of endogenous EPO that accompanies critical illness,⁴⁷ the use of recombinant EPO in critically ill patients has been controversial. Multiple studies using recombinant EPO have shown conflicting results.^{48,49} The use of recombinant EPO may result in a small decrease in RBC transfusion for some patients, but it does not show an overall mortality benefit, and it appears that the risk of thrombotic events likely outweighs the benefits in most critically ill patients.⁴⁹ The one subset of patients that may benefit from recombinant EPO are those with multiple trauma,⁵⁰ but the reason for this is unclear and the practice continues to be controversial.

CONCLUSIONS

Transfusion of blood components can be an essential part of the management of critically ill patients. However, despite the growing body of evidence recommending specific transfusion thresholds and more judicious use of blood products, many transfusion practices continue to be rooted in tradition. Transfusion carries with it multiple risks, including an increased risk of infection, multiple organ failure (MOF), ALI, and mortality for every unit of component administered. Practitioners must have a clear understanding of these risks in order to use blood component therapy safely and effectively.

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Deep Vein Thrombosis

Amy Tortorich • David R. Gens

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INTRODUCTION

In the United States, it is estimated that roughly 100 per 100,000 people per year experience a first-time venous thromboembolism (VTE). Of these cases, two-thirds are caused by deep vein thrombosis (DVT).¹ Much literature has been devoted to the occurrence of VTE in hospitalized patients who are ill or recovering from a surgical procedure. However, many patients present as outpatients to the emergency room with symptoms related to their VTE. This chapter focuses on the current practices for evaluation and diagnosis of DVT and hopes to help guide the emergency physician through the current evidence-based clinical practice guidelines for antithrombotic and thrombolytic therapy.^{2,3}

This second edition update focuses on the following four areas: further literature supporting the use of point-of-care ultrasonography by the emergency medicine physician; diagnosis and management of the upper extremity DVT; the updated 2012 American College of Chest Physicians (ACCP) guidelines regarding diagnosis and treatment of VTE diseases; and oral direct thrombin inhibitors or oral factor Xa inhibitors for the treatment of DVT.

ANATOMY AND PATHOPHYSIOLOGY

Lower extremity DVT is subdivided into proximal (thigh) and distal (calf) vein thrombosis. Proximal DVT is considered of more clinical importance since it is more commonly associated with serious disease and potentially fatal outcomes.

Venous thrombi are composed mainly of fibrin and red blood cells, the number of platelets and leukocytes being variable. The development, progression, and breakdown of VTE reflect a balance between thrombogenic stimuli and protective mechanisms. In the 19th century, Virchow identified and described thrombogenic stimuli. Virchow is credited with outlining the now classic triad of hypercoagulability, endothelial injury, and stasis in association with VTE.⁴ The presence of these factors alters the balance between endogenous fibrinolysis and fibrin formation, which contributes to the formation and proliferation of a thrombus.¹ The protective mechanism against thromboembolic formation are inactivation of activated coagulation factors by circulating inhibitors such as antithrombin and activated protein C, clearance of activated coagulation factors and soluble fibrin polymer complexes by mononuclear phagocytes and the liver, and plasma and endothelial cells derived fibrinolytic enzyme lysis of fibrin.⁵

Using Virchow's triad as framework, one can better understand the factors that predispose the development of venous thrombosis and the protective mechanisms that counter thrombogenic stimuli. This allows for a better understanding of the various risk factors and treatments for venous thrombi.

Hypercoagulability

The activated clotting factors in blood are regulated by inhibitors on the surface of endothelial cells and circulating antiproteinase. Hypercoagulable states offset the balance and tip the natural clotting cascade in the direction of fibrin production and clot formation. This can be seen as a result of reduced levels of inhibitors or an increase in activated clotting factors. Activation of coagulation may result from the contact of factor XII with collagen on the damaged vessels exposed subendothelium.⁶ Malignant cells contain a cysteine protease which can directly activate factor X. This may be one mechanism by which malignancy can induce thrombosis.⁷ Fibrin formation is enhanced by acquired states of hypercoagulability. Genetic thrombophilias and neoplastic abnormalities increase fibrin formation or decrease fibrinolysis.

Vascular Injury

The processes that initiate a venous thrombosis are less certain and felt to be much different from those that initiate an arterial thrombosis. In arterial thrombosis, a clear relationship between blood vessel injury and thrombus formation has been demonstrated. Following the rupture of an atherosclerotic plaque, the endothelial layer of the vessel is lost, thus exposing subendothelial ligands such as von Willebrand factor (VWF) and collagen. Platelets have specific receptors for these ligands and therefore bind, signaling additional cofactors and initiating thrombin formation.^{8,9}

The mechanisms by which damage to the venous vessel wall initiate a thrombus formation are less understood. Gross vessel wall injury does not appear to be a prerequisite for venous thrombi formation. A study of 41 autopsies failed to identify any gross vessel wall injury in 49 of 50 lower extremity thrombi.¹⁰ However, vascular endothelium can be damaged in other ways: endotoxins, inflammatory cytokines, and hypoxia.

Inflammation results in the activation of the endothelium, which leads to the release of granules that contain VWF and membrane-bound P-selectin. These proteins can attach to the endothelial surface as well as bind leukocytes.⁸ Leukocytes, in particular monocytes, are able to synthesize tissue factor (TF).¹¹

Additionally there are animal data suggesting that TF-bearing microvesicles may participate in DVT formation. In a mouse model, elevated levels of leukocyte-derived microvesicles were shown to be associated with greater thrombus mass.¹² Other studies have demonstrated elevated TF antigen levels and TF-VIIa activity in cancer patients.¹³ The increased numbers of TF-bearing microvesicles may play a role in the associated hypercoagulability. This theory is supported by autopsy studies that demonstrated DVT not associated with vessel trauma is frequently bilateral.¹⁴



TABLE 39-1: Risk Factors for Venous Thromboembolism

Patient-specific factors

Prior episode of venous thromboembolism
Increasing age
Obesity
Increased estrogen states
(pregnancy or puerperium, oral contraceptive pills, hormonal therapy)
Immobility
(paralysis, travel, hospital or nursing home resident)

Inherited thrombophilia

Factor V Leiden mutation
Prothrombin gene mutation
Protein S deficiency
Protein C deficiency
Antithrombin (AT) deficiency
Hyperhomocysteinemia

Medical conditions

Stroke
Congestive heart failure
Chronic obstructive pulmonary disease
Neuromuscular weakness syndromes (e.g., Guillain-Barré)
Myocardial infarction
Burns
Malignancy
(higher risk during chemotherapy and radiotherapy)
Medications:
Tamoxifen, Bevacizumab, Thalidomide, Lenalidomide
Lupus anticoagulants/antiphospholipid antibody syndrome

Surgery

Major surgery: abdominal, gynecologic, urologic, orthopedic, neurosurgery
Cancer related surgery

Trauma

Multisystem trauma
Fractures of the hip and pelvis
Major fracture
Spinal cord injury
Spinal fracture

Other

Indwelling central venous catheter
Prolonged mechanical ventilation
Consumptive coagulopathy
Heparin-induced thrombocytopenia

Data from Fields JM and Goyal M. Venothromboembolism. *Emerg Med Clin North Am.* 2008; 26:649–683, viii; Ogawa S, Gerlach H, Esposito C, et al. Hypoxia modulates the barrier and coagulant function of cultured bovine endothelium. Increased monolayer permeability and induction of procoagulant properties. *J Clin Invest.* 1990; 85:1090–1098; and Closse C, Seigneur M, Renard M, et al. Influence of hypoxia and hypoxia-reoxygenation on endothelial P-selectin expression. *Thromb Res.* 1997; 85:159–164.

Additionally, the arterial thrombi cellular composition is different from that of venous thrombi. Platelets compose the core of arterial thrombi and are the cellular components attaching to the vessel wall.¹⁵ Venous thrombi are composed

predominantly of fibrin, and the fibrin-rich regions of the thrombi are found at the site of attachment to the vessel wall.¹⁰ The lack of platelets found at the site of attachment of a venous thrombus could explain why antiplatelet drugs have had limited efficacy for venous thrombosis.⁹

Venous Stasis

Venous stasis leads to an increase in fibrin cross-linking.¹⁶ Contraction of the calf muscles enhances venous return from the lower extremities. Blood is propelled upward, preventing pooling in the legs. Stasis, conversely, leads to a reduction in venous blood flow. Diminished blood flow allows the accumulation of prothrombotic substances (such as thrombin) that otherwise would be washed downstream where they are inactivated. In general, thrombin from the lower extremities is washed into the capillary bed of the lung, which has a large surface area coated with anti-thrombotic substances.⁸

Venous stasis may also lead to local hypoxia. By allowing stagnation of blood, the hemoglobin in the erythrocytes is desaturated, stimulating hypoxia responses in leukocytes, platelets, and endothelial cells.¹⁷ Hypoxia can lead to local ischemia, which has been shown to activate the expression of P-selectin on endothelial cells.¹⁸ It has been proposed that the expression of P-selectin enables the TF-bearing micro-vesicles to initiate coagulation and thrombosis.⁹

RISK FACTORS

There are numerous risk factors that promote the formation of a VTE. The major ones are listed in Table 39-1.^{1,19,20} Ethnicity has also been shown to influence the prevalence of

VTE. Hispanics and Asians have a lower adjusted risk of VTE than do Caucasians and African Americans.^{21,22} Advancing age correlates with an increased rate of thromboembolism. An increased occurrence of VTE is observed with each decade over the age of 60.⁵ Persons under the age of 15 have an incidence of VTE of less than 5 cases per 100,000. After the age of 80, however, the incidence increases to 500 cases per 100,000.^{23,24}

Factor V Leiden is currently recognized as the most common hereditary abnormality predisposing to venous thrombosis. The substitution of glutamine for arginine at residue 506 in the factor V molecule makes factor V resistant to proteolysis by activated protein C.⁵ The gene mutation follows autosomal dominant inheritance and is more prevalent in Caucasians.¹⁴ A patient who is homozygous for the factor V Leiden mutation has a marked increase risk of thromboembolism (estimated 80-fold increase risk) and presents at an earlier age than those who are heterozygous.²⁵ Figure 39-1 shows the coagulation pathway and where circulating inhibitors function to protect against thromboembolic formation. Deficiency in circulating inhibitors leads to increase thrombus formation.

Further risk factors are mentioned in a National Institutes of Health (NIH) conducted case-crossover study using linked databases of the Health and Retirement study. The study was a longitudinal study that gathered data from Medicare beneficiaries and linked them to files from the Centers for Medicare and Medicaid Services (CMS). They looked at triggers of hospitalization for VTE. This study notes infection, erythropoiesis-stimulating agents, and blood transfusion as potential additional risk factors for VTE.²⁶ The authors note venous stasis as a recognized component of the inflammatory response that enables the migration of leukocytes to the site

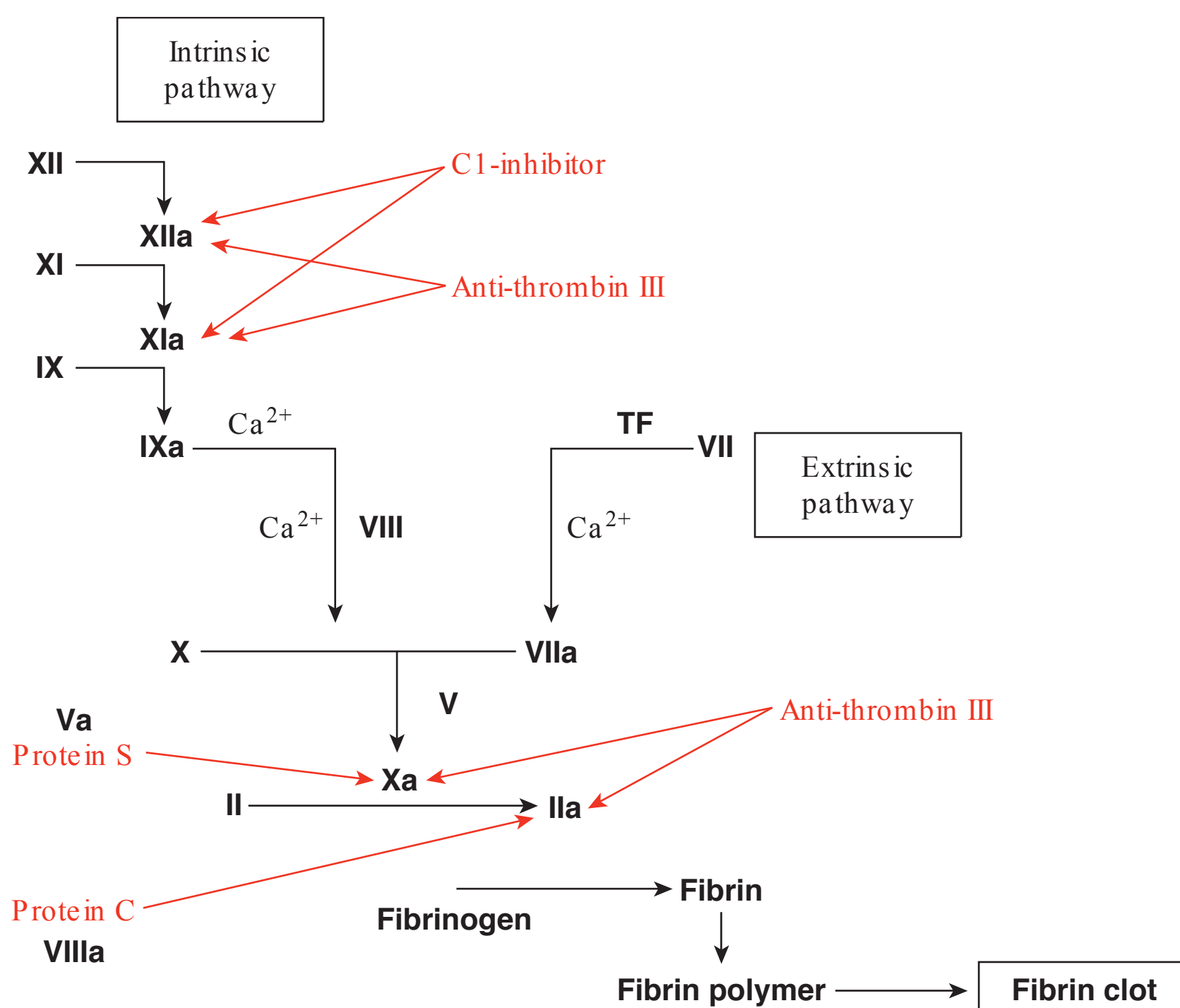


FIGURE 39-1 Blood coagulation cascade. *Black arrows* indicate procoagulant property of a substance. *Red arrows* indicate coagulation inhibiting property of a substance. Deficiency in coagulation inhibiting factors enhances coagulation. Ca²⁺, calcium; TF, tissue factor; a, activated.

of infection. Due to the increased storage of transfused blood, transfused red blood cells have demonstrated greater adhesion to the endothelial cells, with sequestration in the lungs. Erythropoiesis-stimulating agents currently have a black box warning for treatment of patients with cancer, and the Food and Drug Administration (FDA) issued a safety communication regarding their use in patients with chronic kidney disease. This study is particularly relevant to the emergency department because it also makes note of antipsychotic medications being found to have an increased risk of VTE and was most elevated for antipsychotics given by injection.

DIAGNOSIS

Clinical Presentation

The initial symptoms of a DVT are variable and largely non-specific: cramping, a sense of fullness, paresthesia, or pain in the thigh or calf. A physical examination may reveal unilateral swelling, erythema or discoloration, and warmth of the affected extremity; tenderness to palpation; dilation of superficial collateral veins; and a palpable venous cord. The classic Homan's sign (sharp pain in the calf or posterior aspect of the knee on passive dorsiflexion of the foot) is insensitive and non-specific.²⁷ A patient with minor signs and symptoms may have extensive DVT, while someone with severe leg pain and swelling may not have a DVT demonstrated by objective testing. Clinical examination is correct only about 50% of the time.

The subtle and nonspecific presentation of a DVT can make it difficult to clinically differentiate the diagnosis from a broad differential diagnosis. Thus, objective testing is needed to confirm or exclude the diagnosis of DVT. Several objective tests are available for establishing the diagnosis of DVT.

Objective Testing

D-DIMER

D-dimer (DD) units are produced as the fibrinolytic system degrades cross-linked fibrin. They are generated by the action of factor XIIIa on fibrin monomers and polymers. Monoclonal antibodies in DD assays recognize the fragments from cross-linked fibrin. A small percentage of plasma fibrinogen is physiologically converted to fibrin and then degraded. Thus, small amounts of DD are present in healthy individuals. However, increased concentrations are seen in conditions in which fibrin formation is enhanced and subsequently degraded by plasmin. On average, the plasma level is increased eightfold in VTE; moreover, the level falls in parallel with symptom duration and the start of anticoagulant treatment.²⁸ The plasma half-life is approximately 8 hours, and DD fragments are cleared by the kidney and reticulo-endothelial system.²⁹

The detection of the monoclonal antibody-DD fragment complexes is performed by various techniques: enzyme-linked immunosorbent assay (ELISA), immunofiltration, and sandwich-type or agglutination techniques. Describing the various commercial DD assays is beyond the scope of this text. Each diagnostic system has its own cutoff levels. Clinicians

should be knowledgeable of the specific test their facility uses and furthermore only use DD assays that have been appropriately validated in prospective outcome studies.²⁹

A number of clinical conditions increase DD levels: infection, inflammation, cancer, surgery, trauma, extensive burns or bruises, ischemic heart disease, stroke, peripheral artery disease, ruptured aneurysm or aortic dissection, pregnancy, and cerebral sinus thrombosis.²⁸ The diagnostic yield of DD is lower in the elderly because the concentrations of DD rise in the normal aging population. In a cost-effectiveness analysis of a single study of 1,029 patients, one group of investigators demonstrated using DD was cost-saving until the age of 79.³⁰

Of note, in contrast to diagnosing lower extremity DVT, sensitive DD testing has not been prospectively tested in high-quality management studies and thus a low quantitative (or negative qualitative) DD cannot be used to exclude upper extremity DVT (UEDVT).^{31,32}

The objective diagnostic imaging tests currently most useful in diagnosing patients with clinically suspected DVT are ultrasound imaging and venography. Both have been validated through clinical trials that include prospective studies with long-term follow-up establishing the safety of withholding anticoagulation treatment in patients with negative results.

ULTRASOUND

Venous ultrasound (US) has become the standard diagnostic test in patients with a suspected DVT. The two common methods of US used in assessing the presence of DVT are compression US and duplex.

A 2005 meta-analysis examined the diagnostic accuracy of US for DVT as well as performed a separate analysis of different US techniques: compression US only, color Doppler only, continuous wave Doppler only, duplex (combined compression and color Doppler US), and triplex (combined compression, color Doppler and continuous wave Doppler US).³³ This study determined that diagnostic accuracy varies according to the technique used. Optimal sensitivity was demonstrated by using duplex or triplex US. Optimal specificity was seen by using compression US alone. The authors conclude that compression US alone is probably the appropriate technique for patients with a low probability of DVT, whereas when evaluating patients at high risk for DVT or to identify distal DVT, duplex or triplex US would be the appropriate technique.

In compression US, evaluating for a venous thrombosis consists of determining vein patency or the lack thereof (Figure 39-2). To determine venous patency, the gold standard is to determine if the vein collapses completely under pressure, which is directly visualized with US when the lumen disappears entirely (Figures 39-3 and 39-4). Continuous-wave Doppler also evaluates blood flow and direction, but as a graphical depiction.³⁴

A duplex US combines color Doppler with compression US. The color Doppler represents flow within a vein. The specific color maps are assigned to a variety of speeds and one of two directions (toward or away from the US transducer).³⁴

Augmentation is a technique to confirm blood flow through a section of an extremity. It utilizes either pulse-wave

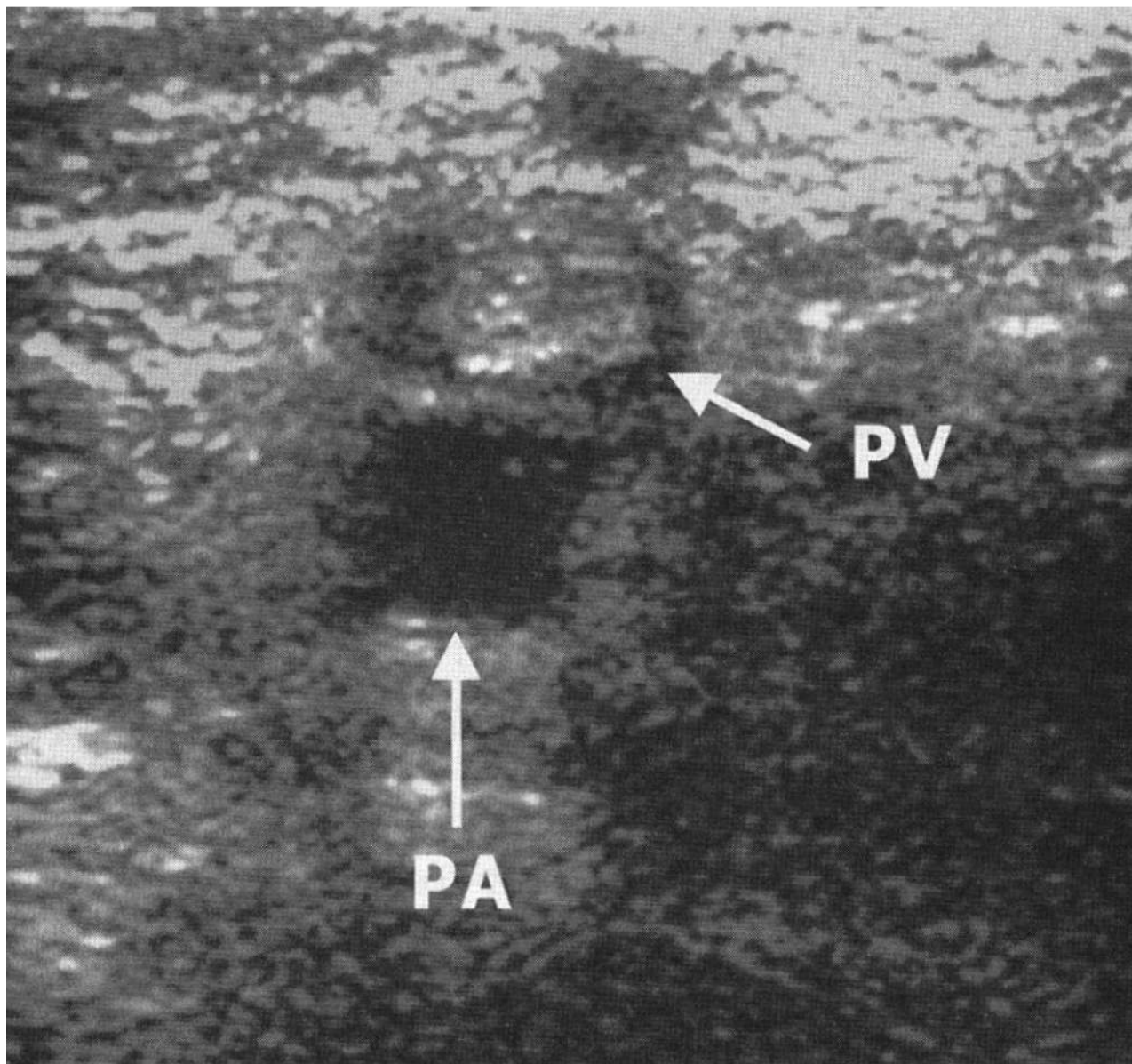


FIGURE 39-2 An echogenic thrombus can be seen within the popliteal vein. PV, popliteal vein; PA, popliteal artery. (Reproduced with permission from Ma OJ, Mateer, JR, & Blaivas M: *Emergency Ultrasound*, 2nd edition. New York: McGraw-Hill Publishing; 2007.)

or color Doppler. While evaluating the proximal portion of a venous segment (for example, the common femoral vein), the sonographer squeezes the calf, which sends a rush of venous blood past the transducer. The increased blood flow is seen on Doppler, which is thought to indicate the absence of a completely occlusive thrombus. Patients with venous disease

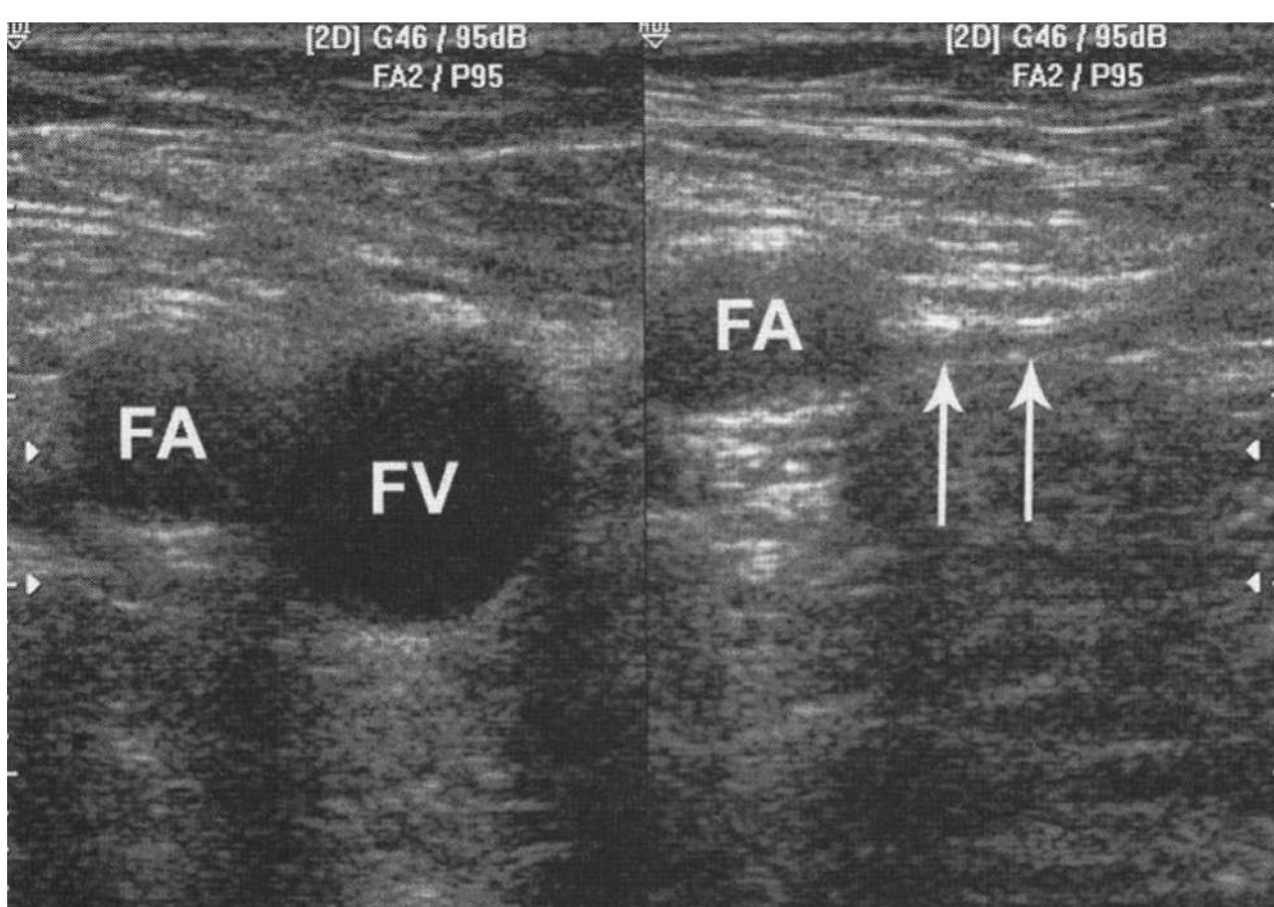


FIGURE 39-3 A split screen showing the common femoral artery (FA) and common femoral vein (FV). The left is without compression. The right is the view after pressure has been applied with the transducer causing the femoral vein to collapse with its wall barely visible (arrows). (Reproduced with permission from Ma OJ, Mateer, JR, & Blaivas M: *Emergency Ultrasound*, 2nd edition. New York: McGraw-Hill Publishing; 2007.)

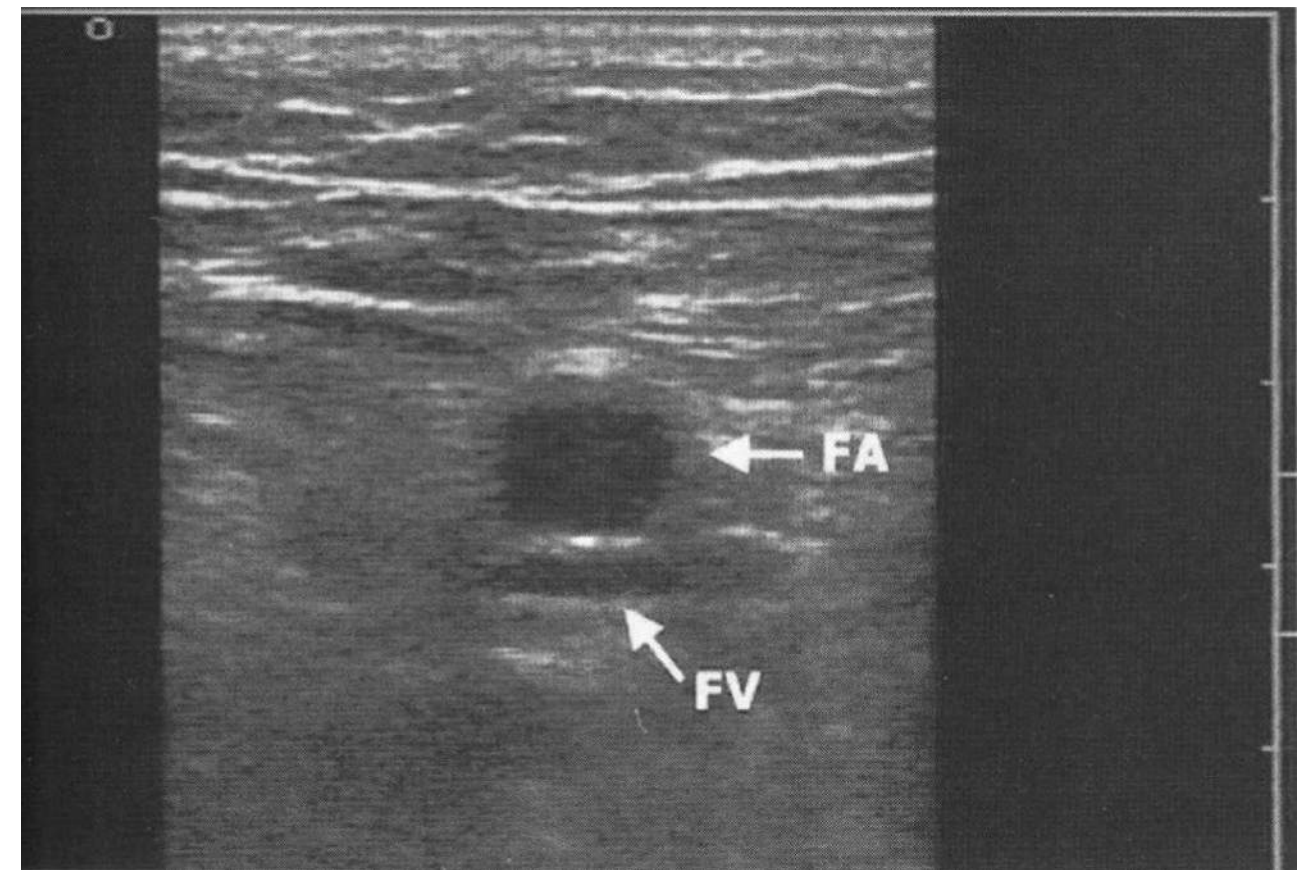


FIGURE 39-4 Incomplete collapse of the femoral vein. If adequate pressure has been applied, this view indicates a thrombus is likely present within the femoral vein. FV, femoral vein; FA, femoral artery. (Reproduced with permission from Ma OJ, Mateer, JR, & Blaivas M: *Emergency Ultrasound*, 2nd edition. New York: McGraw-Hill Publishing; 2007.)

and other comorbidities may lack positive augmentation. Additionally, a partially occluding thrombus or previously established collaterals may still show augmentation.³⁵

When one is risk-stratifying a patient for the presence of DVT, other diagnostic tools such as DD and clinical gestalt are weighed. It is suggested that patients with a negative compression US and a positive DD test should have a repeat compression US within the following week if they are at high risk for DVT.³⁶ This same article mentions that the value of the DD test may decline after the first week for thrombolytic onset, thus necessitating US imaging in patients even with a negative DD test if symptoms persist for longer than a week or for high-risk patients.³⁶

US is the most commonly used initial test for suspected UEDVT. However, direct manual compression cannot be used to evaluate the centrally located brachiocephalic vein and superior vena cava (SVC), nor the medial segment of the subclavian vein underlying the bony clavicle.³¹ Thus a normal US does not exclude UEDVT when there is high clinical suspicion, and additional tests will be needed. A nice review article suggests the following diagnostic algorithm for suspected UEDVT (Table 39-2). Another study of critical care patients demonstrated a specific sonographic sign in 2D images that was present in 20 out of 28 case of acute thrombosis: a double hyperechoic line at the interface between the thrombus and the venous wall³⁷ (Figure 39-5). They speculated that the double hyperechoic line might represent fibrin fibers coating acute clots. This finding could be beneficial in determining thrombus age. Other sonographic features that suggest acute versus chronic thrombosis are as follows. *Chronic thrombosis*: contracted venous segment, thrombus adherence to the venous wall, hyperechoic and heterogeneous appearance of the clot, partial recanalization of the vessel, presence of venous collaterals. *Acute thrombosis*: venous distention, a partially compressible or

 **TABLE 39-2: Suggested Diagnostics for Suspected UEDVT**

Duplex Ultrasound				
Negative		Positive	Incomplete/Nondiagnostic	
Clinical Suspicion (Low)*	Clinical Suspicion (High)*	TREAT	No Alternate Diagnosis	Alternate Diagnosis
- DVT excluded	- Serial Duplex US - CV (CTV or MRV) [‡]		- CV (CTV or MRV) [‡]	- Evaluate alternate diagnosis - Alternate diagnosis excluded - CV (CTV or MRV) [‡]

US, ultrasound; CV, contrast venography; CTV, computed tomography venography; MRV, magnetic resonance venography.
*Suspicion is based on clinician gestalt, as formal clinical prediction tools to quantify the pretest probability of UEDVT are not well validated.
‡CTV or MRV may be chosen in lieu of CV based on institutional experience or patient-specific factors (such as contrast allergy, which would favor MRV).

noncompressible lumen, hyperechoic, homogeneous appearance of clots, and presence of free-floating thrombi.³⁷

**EMERGENCY PHYSICIANS' ROLE IN
US DIAGNOSIS OF DVT**

This area is quite prolific in original research and review articles.^{36,38–41} The utilization of the bedside US examination

by emergency physicians has evolved from a clinical need to improve efficiency of patient care. Many hospitals do not have vascular laboratory services available during off hours. United States-trained emergency physicians are able to quickly scan and interpret images during their initial evaluation without the additional expense and time US technicians require.³⁶ However, emergency physician training on US remains variable across the country.

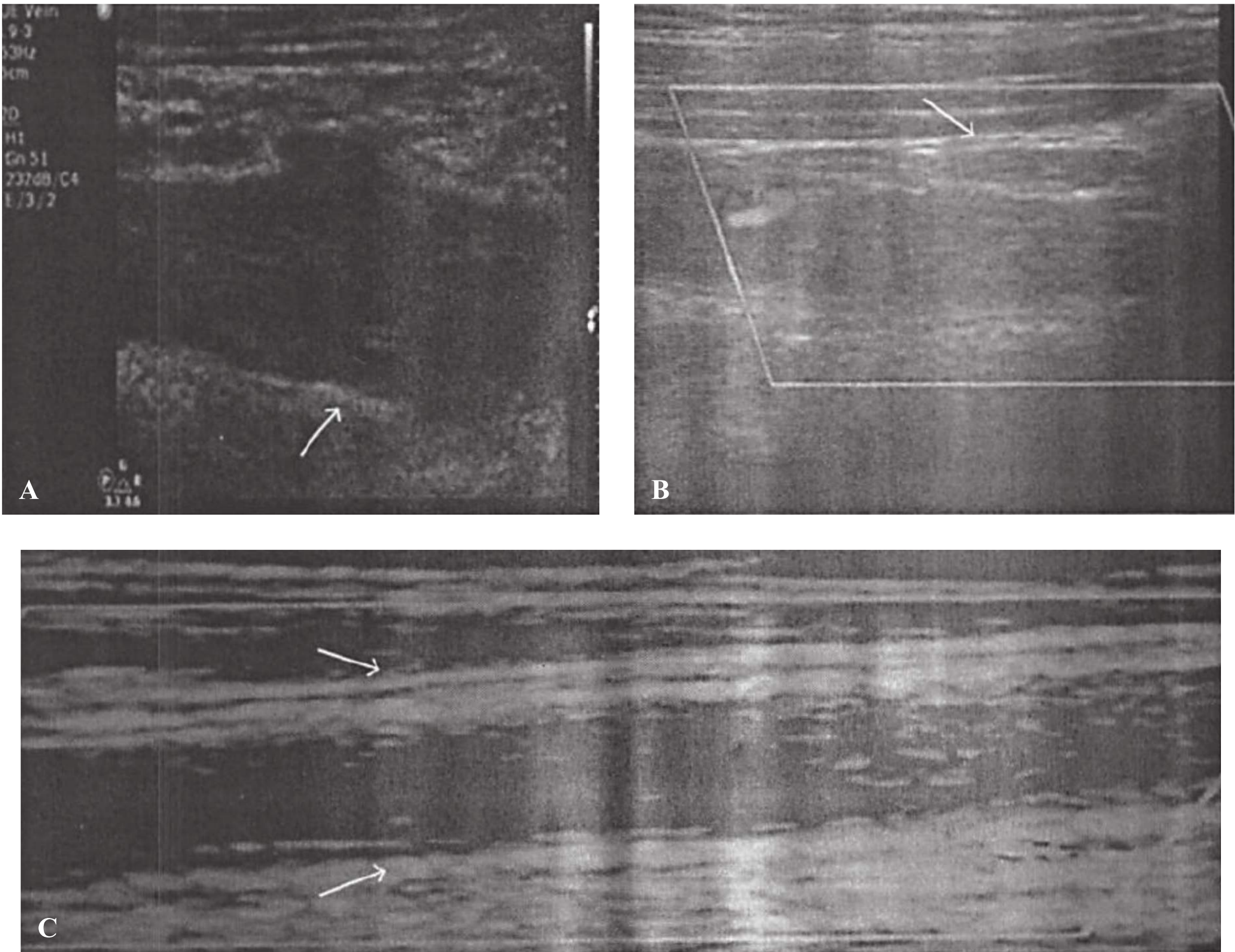


FIGURE 39-5 Double hyperechoic line along fresh thrombus/wall interface (*arrows*) of the subclavian veins (**A** and **B**) and in extended segments of the left brachial vein (panoramic view with zoom) (**C**). Reproduced with permission from Blaivas M, Stefanidis K, Nanas S, et al. Sonographic and clinical features of upper extremity deep venous thrombosis in critical care patients, *Crit Care Res Pract*. 2012;2012:489135.

In the first edition of this text, a study was referenced demonstrating emergency medicine residents having been able to perform a limited duplex examination with good accuracy after limited instruction (90 minutes).⁴² There are now studies showing emergency physicians who receive 10 minutes of training using a low-resolution portable ultrasonographic machine and a 2-point (at the common femoral and popliteal vessels only) compression technique to accurately diagnose proximal lower extremity DVT.³⁹ This article mentions two points of evaluation, but, in the editorial on this article, the author mentions that the goal is to sample both the common femoral and popliteal veins by compressing short segments of the vasculature, typically 3 or 4 cm, with approximately 3 or 4 compressions.³⁸ This same editorial comments that, ideally, the junction of the common femoral vein with the greater saphenous vein is included to identify proximal greater saphenous thrombi that are about to seed the common femoral vein.³⁸ These are treated like a DVT rather than a superficial vein thrombus because of the high likelihood of propagation into the deep venous system.³⁸

The specific amount of training and experience necessary to safely perform point-of-care focused lower extremity ultrasonography to rule out DVT is not yet known. The American College of Emergency Physicians (ACEP) suggests the DVT clinical algorithm in Figure 39-6 but does not specify the amount of training required for the emergency physician performing the bedside ultrasound. In image acquisition, reverse Trendelenburg position in the supine patient is suggested.³⁶

The clinician should be aware of potential limitations of focused lower-extremity US. Although rare, isolated pel-

vic vein DVT accounts for approximately 2% of all DVT cases.^{40,43} A case report is presented in which the focused proximal compression US performed by the emergency physician demonstrated dampened venous pulsation in the common femoral vein at the level of the inguinal ligament, with thrombus noted in the right external iliac vein.⁴⁰ Missing the external iliac DVT is significant because pelvic vein/iliofemoral thrombi have a high risk of embolization and increased risk of post-thrombotic syndrome.^{34,40,44} This article remarks on recognizing clues that a more proximal clot may be present, such as vessel dilation, turbulent flow, or if extreme force is needed to compress the venous structure under interrogation.⁴⁰ Physicians performing point-of-care US will need to be aware of its limitations and educated on subtle findings that indicate abnormal pathology.

Empiric treatment with anticoagulation involves risk, particularly for patients in whom anticoagulation is problematic. Studies have shown that having emergency physicians perform US examinations of the lower extremities themselves decreases time to patient disposition.⁴⁵ The increased ability of emergency physicians to perform a bedside US examination will hopefully decrease the practice of empiric treatment with anticoagulation and serve to help discharge patients more quickly.

CT VENOGRAPHY

Using computed tomography (CT) to diagnose DVT is an area under active investigation. One such example is the PIOPED II study. This prospective multicenter study

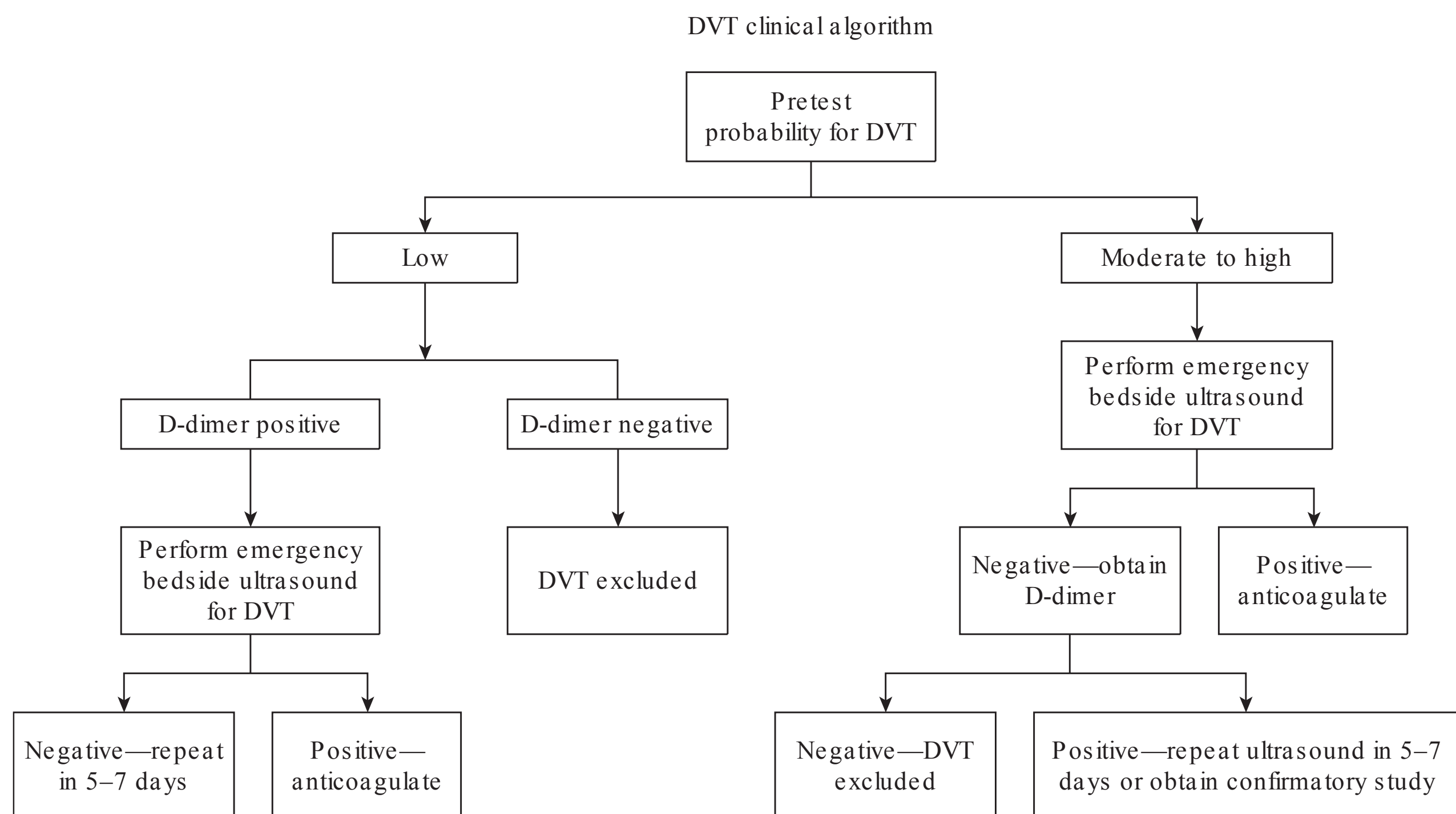


FIGURE 39-6 Reproduced with permission from Fox JC, Bertoglio KC: Emergency Physician Performed Ultrasound for DVT Evaluation, *Thrombosis*. 2011;2011:938709.

of 711 patients compared the clinical value of CT venography (CTV) after multidetector CT (MDCT) angiography (CTA) with venous compression sonography for the diagnosis of VTE.⁴⁶ The investigators demonstrated a 95.5% concordance between CTV and sonography for the diagnosis or exclusion of DVT. They conclude that both studies yield equivalent diagnostic results and that the choice of imaging techniques should be made on the basis of safety, expense, and time constraints.

Protocols that image the pulmonary arteries and the sub-diaphragmatic deep veins (including the legs) should ideally require no additional contrast medium beyond that which is already required for a CT pulmonary angiogram. Yet, not all patients being evaluated for a DVT require a CT pulmonary angiogram. Utilizing CT solely to evaluate for DVT exposes the patient to a radiation dose, potential nephrotoxic intravenous contrast, and the expense of CT.

MR VENOGRAPHY

The diagnostic accuracy of magnetic resonance (MR) venography is comparable to that of contrast venography (CV), yet outcome data are lacking. Additionally, the high cost of MR venography is a limitation for widespread use. Unlike US, MR imaging (MRI) is able to image the pelvic vasculature and vena cava. MRI does not require the use of ionizing radiation, which makes it an attractive option for certain patient populations such as pregnant patients with suspected VTE.

A prospective single-center study of 24 randomly selected patients compared true fast imaging with steady-state precession (FISP) MR venography for suspected DVT with contrast agent-enhanced venography.⁴⁷ The authors conclude that MR venography for DVT is sensitive and specific in the pelvis and thigh but has poor sensitivity below the popliteal vein. Additionally, 11 of the 14 patients without DVT had an alternative diagnosis suggested by MR venography: muscle tear, chronic venous insufficiency secondary to previous DVT, edema and subcutaneous fat/fluid artifact related to clinically confirmed congestive cardiac failure or cellulitis. The ability of MR to provide an alternative diagnosis is an added benefit. MR has some disadvantages: transport of a very sick critical care patient to MR can be difficult, some ventilators are not compatible with MR, and an awake patient may suffer from claustrophobia.

CONTRAST VENOGRAPHY

CV had long been considered the diagnostic test of choice for DVT. However, due to patient discomfort and difficulty in obtaining an adequate study, venography is not recommended as the initial screening test. Noninvasive tests demonstrating equivalent diagnostic accuracy have significantly reduced venography use. Venography is currently reserved for situations in which noninvasive testing is nondiagnostic or impossible to perform. For a CV study to be adequate, complete visualization of the deep venous system (from the calf to the pelvic veins and the inferior vena cava) must be obtained⁴⁸; the internal iliac venous system (hypogastric veins) will not be visualized unless a catheter is directed up

into this system. A constant intraluminal filling defect present in two or more views is the most reliable criterion in diagnosing an acute DVT.⁴⁹

Recommended Diagnosis Strategy for DVT

The executive summary of the antithrombotic therapy and prevention of thrombosis, 9th edition, ACCP guidelines give recommendations regarding diagnosis of suspected DVT.² The recommendations are strong (Grade 1) and weak (Grade 2) based on high-quality (Grade A), moderate-quality (Grade B) and low-quality (Grade C) evidence. Unless otherwise referenced, all recommendations are from the 9th Edition ACCP Evidence-Based Clinical Practice Guidelines.^{2,3} In patients with a suspected first lower extremity DVT, they suggest the choice of diagnostic tests be guided by clinical assessment of pretest probability rather than by performing the same diagnostic tests in all patients (Grade 2B recommendation).

Patients with a LOW pretest probability of first lower extremity DVT

The ACCP guidelines recommend ONE of the following initial tests: a moderately sensitive DD, a highly sensitive DD or compression US (Grade 1B for all comparisons). They suggest initial use of DD testing rather than proximal compression US. They do note that initial testing with US would be preferred if the patient has a comorbid conditions associated with elevated DD levels and is thus likely to have a positive DD (see previous recommendation or reference 28). In patients with a suspected DVT in whom US is impractical (e.g., leg casting, excessive subcutaneous [SC] tissue or fluid prevent adequate assessment of compressibility) or nondiagnostic, CT scan venography, MR venography, or MR direct thrombus imaging are suggested as alternatives to venography.

If the DD is negative, no further testing is recommended. If the proximal compression US is negative, they do not recommend further testing (Grade 1B). If the DD is positive, they suggest further testing with compression US of the proximal veins rather than whole-leg US (Grade 2C).

Patients with a MODERATE pretest probability of first lower extremity DVT

The guidelines recommend ONE of the following tests: a highly sensitive DD, proximal compression US, or whole leg US (Grade 1B). They suggest initial use of a highly sensitive DD rather than US (Grade 2C). The decision of utilizing a highly sensitive DD test or US will depend on the local availability, access to testing, and cost of testing, as well as the probability of obtaining a negative DD if DVT is not present. As above, some patients have comorbidities associated with elevated DD levels. Whole-leg US may be preferred in patients unable to return for serial testing and those with severe symptoms consistent with calf DVT. As above, in patients with a suspected DVT in whom US is impractical or nondiagnostic, CT scan venography, MR venography, or MR direct thrombus imaging are suggested as alternatives to venography.

If the highly sensitive DD is negative, no further testing is recommended (Grade 1B). If the DD is positive, proximal compression US or whole-leg US is recommended (Grade 1B).

If proximal compression US is chosen as the initial test and is negative, a repeat proximal compression US in 1 week OR testing with a moderate or highly sensitive DD assay is suggested (Grade 1C). In patients with a negative proximal compression US but a positive DD, the guidelines recommend repeat proximal compression US in 1 week (Grade 1B). In patients with either a negative serial proximal compression US or a negative single proximal compression US and negative DD, the guidelines recommend no further testing (Grade 1B). If whole-leg US is negative, they recommend no further testing (Grade 1B). If an isolated distal DVT is detected on whole-leg US, they suggest serial testing to rule out proximal extension over treatment (Grade 2C). The guidelines do, however, mention that patients with severe symptoms and risk factors for extension are more likely to benefit from treatment over repeat US.

Patients with HIGH pretest probability of first lower extremity DVT

In those patients with high pretest probability, neither moderately nor highly sensitive DD assays should be used as stand-alone tests to rule out DVT (Grade 1B). The guidelines recommend either proximal compression US, whole-leg US, or venography (Grade 1B). Whole-leg US may be preferred to proximal compression US in certain patients (unable to return for serial testing and those with severe symptoms suggestive of calf DVT). In patients with extensive unexplained leg swelling, no DVT or proximal or whole-leg US and either no DD testing or a positive DD, it is recommended that the iliac veins be imaged to exclude isolated iliac DVT. As above, in patients with a suspected DVT in whom US is impractical or nondiagnostic, CT scan venography, MR venography, or MR direct thrombus imaging are suggested as alternatives to venography.

In patients with a negative proximal compression US, additional testing with either a highly sensitive DD, whole-leg US, repeat proximal compression US in 1 week (all Grade 1B), or venography (Grade 2B) is recommended. Patients with a single negative proximal compression US and a positive DD are recommended to have whole-leg US, repeat proximal compression US in 1 week (both Grade 1B), or venography (Grade 2B). In patients with negative serial proximal compression US, a negative single proximal compression US, and a negative highly sensitive DD, or a negative whole leg US, the guidelines recommend no further testing (Grade 2B for negative whole-leg US and Grade 1B for remaining).

If risk stratification is not done in patients with concern for first lower extremity DVT

The following are recommended as initial testing options: proximal compression US (Grade 1B), whole-leg US (Grade 1B), venography (Grade 1B), or DD testing (Grade 2B).

In patients with a negative proximal compression US, further testing with either moderate or high-sensitivity DD, whole-leg US, or repeat proximal compression US in 1 week is recommended (Grade 1B) or venography (Grade 2B) are options. In patients with a single negative proximal compression

US and a positive DD, further testing with repeat proximal compression US or whole leg US is recommended (Grade 1B). No further testing is recommended in the following patient scenarios: negative serial proximal compression US, a negative DD and negative initial proximal compression US, or negative whole-leg US (Grade 1B).

Patients with suspected recurrent DVT

The guidelines recommend initial evaluation with either proximal compression US or a highly sensitive DD over venography, CT venography, or MRI (all Grade 1B). They remark that initial DD testing with a high-sensitivity assay is preferable if prior US is not available for comparison. If the highly sensitive DD is positive, they recommend proximal compression US (Grade 1B). In patients with suspected recurrent lower extremity DVT and a negative initial proximal compression US, a follow-up proximal compression US (day 7 \pm 1) or testing with a moderately or highly sensitive DD (followed by repeat compression US [day 7 \pm 1] if positive) is recommended (Grade 2B). The proximal compression US is considered negative if normal or residual diameter increases < 2 mm.

In patients with abnormal but not diagnostic US (an increase in residual venous diameter of < 4 but ≥ 2 mm), further testing with venography (Grade 1B) if available, serial proximal compression US (Grade 2B), or testing with a moderately or highly sensitive D-dimer with serial proximal compression US is recommended.

In patients with suspected recurrent ipsilateral DVT who have an abnormal US without a prior result for comparison, further testing is recommended: venography if available (Grade 1B) or highly sensitive DD (Grade 2B) over serial proximal compression US. If the highly sensitive DD is negative, no further testing recommended (Grade 2C). If the highly sensitive DD is positive, venography if available over empirical treatment is recommended (Grade 2C).

Patients with suspected pregnancy-related DVT

Initial evaluation with proximal compression US is recommended. If the initial proximal compression US is negative, further testing is suggested: serial proximal compression US (day 3 and day 7) (Grade 1B) or a sensitive DD (Grade 2B). If the initial compression US and DD are negative or the serial proximal compression US are negative, no further testing is suggested (Grade 1B). Patients with a positive DD are recommended additional follow-up proximal compression US (day 3 and day 7) rather than venography (Grade 1B) or whole-leg US (Grade 2C). If concern for iliac vein thrombosis (swelling of the entire leg, with or without flank, buttock, or back pain) and no evidence of DVT on standard proximal compression, further testing with either Doppler US of the iliac vein (Grade 2C), venography (Grade 2C), or direct MRI (Grade 2C) is recommended over standard serial compression US of the proximal deep veins.

Patients with suspected upper extremity DVT

Initial evaluation with combined modality US (compression with either Doppler or color Doppler) is recommended (Grade 2C). In those patients with suspected UEDVT, a negative initial US, and a high clinical suspicion of DVT, further

testing is suggested: moderate or highly sensitive DD, serial US, or venographic-based imaging (traditional, CT scan, or MRI) (Grade 2C). If the DD, CT, or MRI is negative, no further testing is recommended (Grade 1C). If the DD is positive and no alternative explanation is available for their symptoms, venography is suggested (Grade 2B). For those with an alternative explanation for their symptoms, confirmatory testing and treatment of the alternative explanation is favored over venography (Grade 2C). Just as with lower extremity DVTs, in those patients with comorbid conditions typically associated with elevated DD testing, further radiology testing is preferable.

ADDITIONAL SOURCES OF VENOTHROMBOEMBOLISM

Upper-Extremity DVT

Although the majority of DVTs occur in the lower extremities, upper extremity thrombi are becoming more common than previously thought. UEDVTs involve the subclavian, axillary, or brachial veins. The most common location for UEDVT is found to be in the internal jugular vein (IJV) and superior vena cava (SVC) sites.³⁷ They more commonly are found on the left side and generally occur in more than one segment of the veins at a time. Clinical manifestations are similar to those seen in lower extremity DVT and include edema; dilated collateral veins over the arm, neck, or chest; limb pain; and discoloration.

Pulmonary embolism (PE), recurrent UEDVT, and rarely post-thrombotic (phlebitis) syndrome (PTS) of the arms are all potential complications of UEDVTs.² Symptomatic PE in the setting of UEDVT is reported to range from 3% to 12.4%.^{31,50,51–54} In one registry (RIETE) 9% with UEDVT had symptomatic PE at presentation versus 29% with lower extremity DVT.^{31,55} The rates of new PEs were similar between the two groups during follow-up, however. UEDVT had a higher 3-month mortality (11% vs. 7% in the LE).^{31,55}

There are two forms of upper extremity DVT: (1) primary or (2) secondary thrombosis.

The majority of primary UEDVT cases are caused by anatomic abnormalities of the costoclavicular junction. Effort thrombosis (Paget–von Schrötter syndrome) is due to an underlying chronic venous compression caused by musculoskeletal variations of the thoracic outlet. The subclavian vein can be compressed by a cervical rib or hypertrophied cervical muscles in the athlete (especially in the weight lifter) during Valsalva maneuver (hence “effort” thrombosis): the sudden stasis of blood leads to thrombosis. It is more common in the right arm, likely because this is usually the dominant side and thus involved in more strenuous activity.⁵⁶

In secondary thrombosis, the increased incidence of UEDVT is most likely a result of increased utilization of central venous catheters (CVCs), pacemaker wires, and an increase in treated malignancy.³⁴ CVCs are the predominant cause of secondary UEDVT, and thus the overall incidence of UEDVT is increasing as the use of CVCs, particularly peripherally inserted central catheters (PICCs) is increasing.

A venous catheter is present in about half of UEDVT.^{31,57–59} CVCs trigger thrombus formation through stasis, platelet adherence, and endothelial trauma.^{31,50} Catheter diameter and type (number of lumens), tip location, and concurrent infection affect the risk of DVT. Larger diameter triple-lumen PICCs were shown to carry a 20-fold higher risk of UEDVT when compared to single-lumen PICCs.^{31,60} Peripheral misplacement of the CVC tip has been associated with a 46% thrombosis rate, and concomitant infection confers a relative risk of up to 17.6.³¹ Malignancy is an independent risk factor of UEDVT.⁶¹ Multiple case reports of UEDVT in pregnancy are described in the setting of assisted reproductive techniques and ovarian hyperstimulation syndrome.^{31,62} Total parenteral nutrition (TPN) infusion itself may be a risk factor. The TPN is speculated to be an irritant to the vein causing vascular injury and inflammation that is prothrombotic.^{37,63}

No significant difference was found between internal jugular and subclavian access in thrombotic complications,⁶¹ whereas, femoral access does demonstrate more thrombosis.

In placing a CVC, there are factors that one ought to consider to help minimize thrombosis formation. One should choose the smallest diameter catheter compatible with the indication, assure appropriate position of the catheter tip in the SVC or at the cavo-atrial junction, and remove the catheter promptly when no longer needed. There are studies in the pediatric population showing benefit of heparin-bonded catheters in preventing catheter-related thrombosis.^{31,64,65} In regards to pharmacologic prophylaxis, the ACCP guidelines recommend against routine use of anticoagulant prophylaxis solely on the basis of an indwelling CVC.²

May-Thurner Syndrome

May-Thurner syndrome is an anatomic pattern in which hemodynamically significant compression of the left common iliac vein occurs between the overlying right common iliac artery and the underlying vertebral body. Most commonly it is seen in women between the ages of 20 and 50. Typically, it presents either as chronic venous insufficiency or a large iliofemoral DVT. The diagnosis should be considered in patients with recurrent left lower extremity DVT or chronic, refractory DVT of the left lower extremity. DVT episodes associated with May-Thurner syndrome can be recurrent and/or not respond to treatment with anticoagulation by itself. Treatment can require catheter-directed thrombolysis, venous angioplasty, and/or intravascular stenting.⁶⁶

Phlegmasia Cerulea Dolens

Phlegmasia cerulea dolens is an uncommon form of massive proximal (iliofemoral) venous thrombosis of the lower extremities. Venous obstruction results, leading to a sharp rise in venous pressure, massive interstitial fluid shifts, decreased arterial perfusion due to vasospasm from inflammation, compartment syndrome, and gangrene.¹ This results in a lower extremity that is tense, cool, swollen, painful, and cyanotic (Figure 39-7).⁶⁷ The resulting gangrene,



FIGURE 39-7 Phlegmasia dolens. The left leg is noted to have a bluish discoloration and swelling. (Reproduced with permission from Knoop KJ, Stack LB, Storrow AB: *Atlas of Emergency Medicine*, 2nd edition. New York: McGraw-Hill Professional; 2002.)

compartment syndrome, and arterial compromise can lead to circulatory collapse and shock. Systemic anticoagulation should not be delayed because death or loss of the limb may result. Intravenous thrombolytic therapy's role in treatment is controversial. Emergency thrombectomy should be considered.

TREATMENT

The ACCP published its first consensus statement on antithrombotic therapy in 1986. The most recent ACCP guidelines were released in 2012. This section aims to summarize the 2012 ACCP guidelines on therapy for VTE with regards to application to patients seen by the emergency medicine physician. Unless otherwise referenced, all recommendations are from the 9th Edition ACCP Evidence-Based Clinical Practice Guidelines.^{2,3} The recommendations are strong (Grade 1) and weak (Grade 2) based on high-quality (Grade A), moderate-quality (Grade B), and low-quality (Grade C) evidence.

Briefly, before considering the use of anticoagulant therapy one must consider if the patient has any contraindications to anticoagulation. The absolute contraindications to anticoagulation treatment include severe active bleeding; intracranial bleeding; recent brain, eye, or spinal cord surgery; and

malignant hypertension. Relative contraindications include recent cerebrovascular accident, active gastrointestinal tract bleeding, recent major surgery, severe hypertension, severe renal or hepatic failure, and severe thrombocytopenia (platelets $< 50,000/\mu\text{L}$).⁵

Initial Anticoagulation of Acute DVT of the Leg

The main therapy of acute DVT of the leg is anticoagulation. In patients with a high clinical suspicion of acute VTE, treatment with parenteral anticoagulants is suggested while awaiting the results of diagnostic tests (Grade 2C). For an intermediate clinical suspicion of VTE and results of diagnostic tests expected to be delayed > 4 hours, parenteral anticoagulants are suggested (Grade 2C). For low clinical suspicion of acute VTE and provided test results are expected within 24 hours, no treatment is suggested (Grade 2C).

Options are available for the initial treatment of DVT: (1) SC low-molecular-weight heparin (LMWH) without monitoring; (2) intravenous (IV) unfractionated heparin (UFH) with monitoring; (3) SC UFH given based on weight initially, with monitoring; (4) SC UFH given based on weight initially, without monitoring; (5) SC fondaparinux given without monitoring; and (6) dabigatran, rivaroxaban, or apixaban given orally.

Initial treatment of this disease aims to prevent thrombus extension as well as early and late recurrences of VTE. As patients treated with vitamin K antagonist (VKA) alone have a high rate of recurrence/extension due to the initial hypercoagulable state induced by lowering proteins C and S levels, it is recommended that heparin (or LMWH or fondaparinux) is started along with VKA at the time of diagnosis.⁶⁸ In patients with acute DVT of the leg, early initiation of VKA (e.g., the same day as parenteral therapy is started) is recommended. In regards to VKA therapy in the outpatient, the guidelines suggest initiating VKA therapy with warfarin 10 mg daily for the first 2 days followed by dosing based on international normalized ratio (INR) measurements (Grade 2C). Continue parental anticoagulation for a minimum of 5 days and until the INR is ≥ 2.0 for at least 24 hours (Grade 1B). This recommendation is based on the observation that, regardless of the INR, factor II activity is not significantly reduced earlier than 5 days after starting warfarin. The combination of a relatively long half-life of factor II and the short half-life of protein C and protein S is thought to provoke a paradoxical hypercoagulable state if heparin/LMWH/fondaparinux are stopped prematurely.⁶⁸

In choosing the initial anticoagulant regiment in patients with proximal DVT, the guidelines suggest LMWH or fondaparinux over IV UFH (Grade 2C) and over SC UFH (Grade 2B for the LMWH; Grade 2C for fondaparinux).

LOW-MOLECULAR-WEIGHT HEPARIN

The guidelines prefer LMWH SC to treatment with IV UFH. The guidelines suggest once- over twice-daily administration

of LMWH (Grade 2C). For patients receiving LMWH with severe renal insufficiency (calculated creatine clearance < 30 mL/min, a reduction of the dose is suggested; Grade 2C).

IV UNFRACTIONATED HEPARIN

The guidelines recommend bolus and infusion be weight-adjusted. Bolus 80 units/kg followed by 18 units/kg/hour. Or use a fixed dose (bolus 5,000 units followed by 1,000 units/hour rather than alternative regimens; Grade 2C).

SC UNFRACTIONATED HEPARIN

For outpatients treated with SC UFH, weight-adjusted dosing (first dose 333 units/kg, then 250 units/kg) *without* monitoring. This is favored over fixed or weight-adjusted dosing with monitoring (Grade 2C).

FONDAPARINUX

Fondaparinux is a synthetic pentasaccharide. Like LMWH, it can be administered SC without monitoring and has been shown to be effective in the treatment of acute DVT. The disadvantage of fondaparinux is a prolonged half-life (17 hours) and the absence of an antidote. If the patient's body weight is > 100 kg, an increased dose is suggested from the usual 7.5–10 mg (Grade 2C).

Direct Oral Anticoagulants

Direct oral anticoagulants (DOACs) for the treatment of DVT are a developing area since the original edition of this text. This new generation of oral anticoagulants includes direct thrombin inhibitors (DTI) such as dabigatran and direct factor Xa inhibitors such as rivaroxaban, apixaban, and edoxaban. These drugs affect the enzymatic activity of procoagulant enzymes as compared to VKAs that influence the hepatic synthesis of coagulation factors. These drugs are not dependent on endogenous antithrombin, whereas the heparin and heparin analogues such as fondaparinux are.⁶⁹ DTI and factor Xa inhibitors “generally display a linear relation between plasma concentrations of the drug and anticoagulant activity, with reliable pharmacokinetics and pharmacodynamics.”⁶⁹

They have a rather short half-life and do not share the relevant properties with heparin, thus heparin-induced thrombocytopenia (HIT) should not be an issue. Dabigatran, rivaroxaban, and apixaban can be used in patients with earlier HIT; however, treatment of acute newly diagnosed HIT is currently discouraged due to lack of clinical trials, data, and dose recommendations for this indication.⁶⁹

The current 2012 ACCP guidelines have sparse information on the DOACs. Most likely future updated guidelines will have more information and recommendations on their use. Moreover, in my literature review, it appears that the Cochrane collaboration is undergoing a review on oral DTI or oral factor Xa inhibitors for the treatment of DVT. All that was available to me at the time of this publication is their protocol.⁷⁰ The following section is taken mostly from the Cochrane protocol article.

ORAL DIRECT THROMBIN INHIBITORS

Oral DTIs work by binding directly to the enzyme thrombin without the need for a co-factor, such as antithrombin. DTIs inhibit both soluble thrombin and fibrin-bound thrombin.^{70,71} Their anticoagulant effect is more predictable due to their lack of binding to other proteins, an antiplatelet effect, and the absence of HIT.^{70,72} Two DTI, dabigatran and ximelagatran, are mentioned in the Cochrane protocol. Ximelagatran caused unacceptable liver toxicity and thus was never licensed.

Dabigatran

Dabigatran etexilate is a reversible oral DTI that is metabolized to dabigatran, its active ingredient, in the gastrointestinal tract.^{70,73} It effectively binds to free thrombin and clot-bound thrombin.⁶⁹ It requires an acidic pH. No anticoagulation monitoring is required. It is associated with a lower incidence of intracranial hemorrhage in comparison with VKA but has shown a higher incidence of indigestion and heartburn, as well as a higher incidence of gastrointestinal bleeding.⁷⁰ It is predominantly renally excreted, and, unlike the other DOACs, hemodialysis can eliminate dabigatran from the body.⁶⁹ It is contraindicated in patients with a creatinine clearance of < 30 mL/min.

For treatment of venous thrombosis, dabigatran is used at dose of 150 mg twice daily.^{69,74} Dabigatran is approved for prophylaxis as well as treatment of DVT/PE.

ORAL FACTOR Xa INHIBITORS

Oral factor Xa inhibitors bind directly to the active site of factor Xa subsequently blocking the activity of this clotting factor. Unlike indirect factor Xa inhibitors (example fondaparinux), direct factor Xa inhibitors “inactivate free FXa and FXa incorporated with the prothrombinase complex equally well” and do not require interaction with the inhibitor antithrombin.^{70,75} They do not require regular blood test monitoring, have been shown to be noninferior to VKA, appear to have fewer drug interactions compared to VKA, and have shown no food or alcohol interactions.⁷⁰

Rivaroxaban

Rivaroxaban is a reversible oral direct factor Xa inhibitor. It is approved for the treatment of acute DVT. The recommended dosing is 15 mg twice daily for the first 21 days followed by 20 mg once daily for continued treatment and prevention of recurrence.^{70,76} Impaired renal function results in an enhanced effect of rivaroxaban. With a creatinine clearance of 15–50 mL/min, the dose is reduced to 15 mg daily and is contraindicated in patients with a creatinine clearance of < 15 mL/min.⁶⁹ Rivaroxaban is approved for DVT prophylaxis, DVT/PE prophylaxis, recurrent DVT/PE prophylaxis, and DVT/PE treatment.

Apixaban

Apixaban (Eliquis) is absorbed as an active substance and thus does not require biotransformation.^{69,77} Twice-daily dosing resulted in a more constant anticoagulant effect and less

fluctuation.^{69,77} In patients with at least two of the following characteristics—age ≥ 80 years, body weight ≤ 60 kg, or serum creatinine ≥ 1.5 mg/dL—a reduced dose of 2.5 mg twice daily is recommended.⁶⁹ It is not recommended in patients with a creatinine clearance < 15 mL/min or in those undergoing dialysis. Eliquis is approved for DVT prophylaxis, DVT/PE prophylaxis recurrent, and DVT/PE treatment.

Additionally, betrixaban and edoxaban are listed as oral factor Xa inhibitors in the Cochrane protocol but because they are not approved for use at the time of this publication, I will not discuss them further.

For all of the DOACs, additional studies are needed, particularly in special populations: elderly, adolescents, those with impaired renal function, extremes of body pain, and potentially interfering medications such as NSAIDs and antiplatelet therapy. Moreover, patients with distal DVT, DVT of the upper limbs, superficial thrombophlebitis, catheter-related thrombosis, and patients who underwent thrombolysis have not been studied.⁷⁸ Additionally, many physicians who have strong concerns regarding this new class of DOACs in regards to the ability to quickly reverse their effects in a patient who develops bleeding (such as major trauma, intracranial hemorrhage, and gastrointestinal bleeding).

CHOICE OF ANTICOAGULANT REGIMEN FOR LONG-TERM THERAPY

- DVT of the leg and no cancer: VKA therapy is suggested over LMWH for long-term therapy (Grade 2C). For DVT of the leg and no cancer who are not treated with VKA therapy, they suggest LMWH over dabigatran or rivaroxaban for long-term therapy (Grade 2C).
- DVT of the leg and cancer: suggest LMWH over VKA therapy (Grade 2B). If not treated with LMWH, they suggest VKA over dabigatran or rivaroxaban for long-term therapy (Grade 2B).
- These ACCP guidelines were being prepared in October 2011 and, at that time, there were insufficient data; however, the authors note new data are rapidly emerging, particularly in regards to DOACs.
- In patients with acute symptomatic DVT of the leg, the guidelines suggest the use of compression stockings (Grade 2B). Compression stockings are to be worn for 2 years and beyond that if patients have developed PTS.

Isolated Distal DVT

If the patient is without severe symptoms or risk factors for extension, serial imaging of the deep veins for 2 weeks is suggested over initial anticoagulation (Grade 2C). If the patient has severe symptoms or risk factors for extension, however, initial anticoagulation over serial imaging of the deep veins is then suggested (Grade 2C). It is mentioned though, that patients at high risk for bleeding are more likely to benefit from serial imaging. In those patients with acute isolated distal DVT of the leg who are treated with initial

anticoagulation, the same approach is utilized as for patients with acute proximal DVT (Grade 1B). For patients with acute isolated distal DVT of the leg who are managed with serial imaging: if the thrombus doesn't extend, then no anticoagulation (Grade 1B); if the thrombus extends but remains confined to the distal veins, then anticoagulation is suggested (Grade 2C); if the thrombus extends into the proximal veins, then anticoagulation is recommended (Grade 1B).

Superficial Vein Thrombosis

In patients with superficial vein thrombosis of the lower limb of at least 5 cm in length, the guidelines suggest the use of a prophylactic dose of fondaparinux or LMWH for 45 days (Grade 2B). They suggest fondaparinux 2.5 mg daily over a prophylactic dose of LMWH (Grade 2C).

Acute VTE During Pregnancy

The guidelines recommend therapy with adjusted-dose SC LMWH over adjusted-dose UFH (Grade 1B). Antenatally, LMWH is recommended over VKA treatment (Grade 1A). Anticoagulation should be continued for at least 6 weeks postpartum (for a minimum total duration of therapy of 3 months) (Grade 2C). The guidelines go into many other areas of VTE and pregnancy such as recurrent VTE, thrombophilia, and mechanical heart valves. I will not address these areas currently because they are not high yield for the clinician in the emergency department diagnosing VTE.

VTE in Children

For children with first VTE, central venous access device (CVAD) and non-CVAD related, it is recommended to acutely anticoagulate with either UFH or LMWH (Grade 1B). Initial treatment is with UFH or LMWH for at least 5 days (Grade 1B). In regards to ongoing therapy, LMWH or UFH is also recommended. In patients in whom clinicians will subsequently prescribe VKAs, oral therapy is recommended to begin as early as day 1, discontinuing UFH/LMWH on day 6 or later if the INR has not exceeded 2.0 (Grade 1B). For children with idiopathic VTE, anticoagulant therapy is suggested for 6–12 months (Grade 2C). For children with secondary VTE (VTE occurring in association with a clinical risk factor) and the risk factor has resolved, anticoagulant therapy is suggested for 3 months (Grade 2C). In children who have ongoing but potentially reversible risk factors, continued anticoagulant therapy beyond 3 months is suggested in either therapeutic or prophylactic doses until the risk factor has resolved (Grade 2C). In children with recurrent idiopathic VTE, we recommend indefinite treatment with VKAs (Grade 1A). In recurrent secondary VTEs with an existing reversible risk factor, anticoagulation is suggested until resolution of the precipitating factor for a minimum of 3 months (Grade 2C).

In children found to have a VTE with CVAD in place, the CVAD is only recommended for removal if nonfunctioning or no longer required (Grade 1B). At least 3–5 days of

anticoagulation therapy is suggested prior to removal of the CVAD. If there is still need for CVAD and the catheter is still functioning, the guidelines suggest the CVAD remain in situ and the patient be given anticoagulants (Grade 2C). If the CVAD remains necessary after the initial 3 months of therapy, a prophylactic dose of VKAs (INR range, 1.5–1.9) or LMWH (0.1–0.3 units/mL) be given until the CVAD is removed (Grade 2C).

Thrombolysis in pediatric patients is only suggested for life- or limb-threatening thrombosis (Grade 2C). Additionally in life-threatening VTE, thrombectomy is suggested (Grade 2C). In children who have had a thrombectomy, anticoagulant therapy is suggested following the general recommendations for management of VTE in children with cancer (Grade 2C).

Supra Therapeutic INRs

- **Vitamin K for patients taking VKAs with high INRs without bleeding**
 - INR between 4.5 and 10: suggest against the routine use of vitamin K (Grade 2B).
 - INR > 10: suggest oral vitamin K be administered (Grade 2C).
- **Treatment of anticoagulant-related bleeding**
 - VKA-associated major bleeding: suggest rapid reversal of anticoagulation with four-factor prothrombin complex concentrate rather than with plasma (Grade 2C).
 - Additionally, vitamin K 5 to 10 mg by slow IV injection is suggested over reversal with coagulation factors alone (Grade 2C).

TREATMENT STRATEGIES OF THROMBUS REMOVAL FOR ACUTE DVT

Actively removing the thrombi has the potential to decrease acute symptoms and the risk for PTS, and it can be limb-saving in phlegmasia cerulea dolens. By removing the thrombus, venous obstruction is reversed and valvular function is restored, which may prevent late development of venous valvular incompetence. The guidelines further speculate that thrombus removal and subsequent relief of venous obstruction may reduce the risk of recurrent VTE. DVTs involving the iliac and common femoral veins are at the highest risk for PTS and thus are mentioned as a subset with the greatest potential to benefit from thrombus removal.^{3,79}

A recent 2014 Cochrane review⁸⁰ lists several advantages to thrombolysis over standard anticoagulation therapy: more frequent complete clot breakdown as the clot is dissolved, venous patency or blood flow was better maintained, and fewer patients developed PTS. The reduction in PTS was significant, with a reduction by a third with the use of thrombolysis and a number needed to treat of five. This review states that catheter-directed thrombolysis is currently favored because the risk of systemic bleeding may be reduced. In regards to

different agents for thrombolysis, streptokinase was the most widely studied. As expected, there was an increased risk of bleeding, but the risk has decreased over time with the utilization of stricter exclusion criteria. The ACCP guidelines, however, suggest anticoagulant therapy alone over thrombolysis.^{2,3}

Catheter-Directed Thrombolysis

In patients with acute proximal DVT of the leg, the guidelines suggest anticoagulant therapy alone over catheter-directed thrombolysis (CDT) (Grade 2C). The text notes that the risks and benefits with CDT are uncertain and that anticoagulant therapy alone is acceptable. The patients most likely to benefit from CDT are those who attach a high value to preventing PTS versus a lower attached value to complexity, cost, and risk of bleeding with CDT. The guidelines state that CDT may be beneficial in select patients: those with symptoms present for < 14 days, iliofemoral DVT, life expectancy ≥ 1 year, good functional status, and demonstration of a low risk of bleeding. Patients who have undergone successful CDT are still recommended the same intensity and duration of anticoagulant therapy as recommended for those patients who do not receive CDT (Grade 1B).

Systemic Thrombolytic Therapy

Anticoagulant therapy alone is also suggested over systemic thrombolysis (Grade 2C). The text mentions systemic thrombolysis has the potential to reduce PTS but at the expense of an increase in major bleeding. The guidelines state “we believe that systemic thrombolysis should be considered only in patients that meet all of the following criteria: iliofemoral DVT, symptoms < 14 days, good functional status, life expectancy of ≥ 1 year, and low risk of bleeding.”

Operative Venous Thrombectomy

Operative venous thrombectomy for acute proximal DVT is not suggested except for iliofemoral DVT. For patients with acute iliofemoral DVT, good functional status, life expectancy of ≥ 1 year, and symptoms present for < 7 days, the guidelines suggest operative venous thrombectomy to decrease acute symptoms as well as post-thrombotic morbidity at institutions with appropriate expertise and resources. However, if patients do not have a high risk of bleeding, the guidelines suggest that CDT is generally preferable to operative venous thrombectomy. After undergoing operative venous thrombectomy, the guidelines recommend the same intensity and duration of anticoagulant therapy as for those not undergoing venous thrombectomy (Grade 1B).

Vena Caval Filters for the Patient with a DVT

The placement of an inferior vena cava (IVC) filter is not without risk. IVC thrombosis can occur in up to 5% of patients after placement of the filter.⁶⁸ Currently, no randomized trial

has evaluated the efficacy of IVC filters alone (without concurrent anticoagulation) in preventing PE in those with an acute DVT. The guidelines differentiate their recommendations for vena cava filter placement based on the ability to utilize anticoagulation.

- In patients with acute DVT of the leg, the guidelines recommend against the use of an IVC filter in addition to anticoagulants (Grade 1B).
- In patients with acute proximal DVT of the leg who have a contraindication to anticoagulation, then they recommend the use of an IVC filter (Grade 1B).
- In patients with an acute proximal DVT of the leg who have had an IVC filter inserted as an alternative to anticoagulation, they suggest a conventional course of anticoagulant therapy if their risk of bleeding resolves (Grade 2B).
- They do not consider a permanent IVC filter in and of itself as an indication for extended anticoagulation.

DURATION OF ANTICOAGULANT THERAPY

In patients with acute VTE, long-term therapy is recommended over stopping anticoagulation after 1 week of initial therapy (Grade 1B). The text mentions anticoagulant therapy should be continued until (1) the reduction of recurrent VTE no longer outweighs the increased risk of bleeding or (2) patient preference (which they mention may be influenced by financial burden). Risk of recurrence is largely determined by two factors: (1) whether the acute episode of VTE has been effectively treated and (2) the patient's intrinsic risk of having a new episode of VTE. The most important factors that influence risk of recurrence of VTE are presence of a reversible provoking risk factor, unprovoked VTE, and active cancer. Among those with VTE provoked by a reversible factor, the risk of recurrence is much lower if the provoking factor was recent surgery in comparison to nonsurgical triggers (estrogen therapy, pregnancy, leg injury, flight of > 8 hours).

- In patients with proximal DVT of the leg provoked by surgery, treatment with anticoagulation for 3 months is recommended (Grade 1B).
- In patients with proximal DVT of the leg provoked by a nonsurgical transient risk factor, treatment with anticoagulation for 3 months is recommended (Grade 1B).
- In patients with an isolated distal DVT of the leg provoked by surgery or by a nonsurgical transient risk factor, anticoagulation for 3 months is recommended (Grade 1B).
- In patients with an unprovoked DVT of the leg (distal or proximal), treatment with anticoagulation for at least 3 months is recommended (Grade 1B). Then, after the 3 months of treatment, the risk-benefit ratio of extended therapy should be evaluated.
- In patients with a first unprovoked VTE and a high bleeding risk, the guidelines recommend 3 months of anticoagulant therapy.

- In patients with a first VTE that is unprovoked and an isolated distal DVT of the leg, 3 months of anticoagulation is suggested if the bleeding risk is low or moderate (Grade 2B) or high risk (Grade 1B).
- In patients with a second unprovoked VTE, recommendations are based on bleeding risk.
 - Low bleeding risk, recommend extended anticoagulation over 3 months (Grade 1B).
 - Moderate bleeding risk, suggest extended anticoagulation over 3 months (Grade 2B).
 - High bleeding risk, suggest 3 months of anticoagulation (Grade 2B).
- If the risk of bleeding is not high in patients with DVT of the leg and active cancer, extended anticoagulation therapy over 3 months is recommended (Grade 1B). If the bleeding risk is high, extended anticoagulant therapy is still recommended but only a Grade 2B recommendation.
- In patients with DVT of the leg without cancer, VKA therapy is suggested over LMWH for long-term therapy (Grade 2C). If not treated with VKA therapy, LMWH over dabigatran or rivaroxaban for long-term therapy is suggested (Grade 2C).
- In patients with DVT of the leg and cancer, LMWH is suggested over VKA therapy (Grade 2B). If not treated with LMWH, VKA therapy is suggested over dabigatran or rivaroxaban for long-term therapy (Grade 2B).

Intensity of Anticoagulant Effect

- The guidelines recommend that the dose of VKA should be adjusted to maintain a target INR of 2.5 (range 2.0–3.0) for all durations of treatment (Grade 1B).
- For patients with antiphospholipid syndrome with previous VTE, the ACCP guidelines suggest VKA therapy titrated to a moderate intensity INR range (INR 2.0–3.0 rather than higher intensity INR 3.0–4.5; Grade 2B).

TREATMENT OF ACUTE UPPER EXTREMITY DVT

Patients with acute UEDVT are recommended the same 3-month course of anticoagulant therapy with therapeutic doses of LMWH, UFH, or fondaparinux as described for lower extremity DVT. For UEDVT that involve the axillary or more proximal veins, the guidelines recommend acute treatment with parenteral anticoagulation (LMWH, fondaparinux, IV UFH, or SC UFH; Grade 1B). They suggest LMWH or fondaparinux over IV UFH (Grade 2C) and over SC UFH (Grade 2B). Furthermore, they suggest anticoagulant therapy alone over thrombolysis (Grade 2C). For the patient who does undergo thrombolysis, the same intensity and duration of anticoagulant therapy is recommended as for those who do not undergo thrombolysis (Grade 1B).

In most patients with UEDVT that is associated with a CVC, they suggest *against* removing the catheter if it is functional and there is an ongoing need for the catheter

(Grade 2C). The minimum duration of anticoagulation is 3 months (Grade 2B) for both those in which the catheter is left in place as well as those who have the CVC removed. In patients with UEDVT associated with a CVC, 3 months of anticoagulation is recommended in patients without cancer (Grade 1B) and suggested in patients with cancer (Grade 2C).

Uncertainty exists about the need to prescribe anticoagulants to those with thrombus confined to the brachial vein. Acceptable alternatives to full-dose anticoagulants are listed as clinical or US surveillance to detect extension of UEDVT while withholding anticoagulation, treatment with prophylactic-dose anticoagulation, or treatment with therapeutic dose anticoagulation for less than 3 months. The guidelines favor anticoagulation if the isolated brachial vein thrombosis is symptomatic, associated with a CVC that will remain in place, or associated with cancer.

NOACs such as DTIs and Xa inhibitors have not yet been studied for the treatment of UEDVT. In regards to thrombolytic therapy for treatment of UEDVT, the guidelines suggest that thrombolysis should be considered “only in patients who meet all of the following criteria: severe symptoms, thrombus involving most of the subclavian vein and axillary vein, symptoms for < 14 days, good functional status, life expectancy of ≥ 1 year, and low risk for bleeding.” Catheter-based therapy is encouraged over systemic thrombolysis.

Home Versus In-Patient Treatment for DVT

A 2007 Cochrane review concluded that home management is both cost-effective and preferred by patients.⁸¹ Six randomized controlled trials (RCT) involving 1,708 patients compared home (LMWH) to hospital (LMWH or UFH) treatment for DVT. Patients treated at home with LMWH were less likely to have recurrence of VTE and had lower mortality and fewer major bleeds. However, the home treatment patients were more likely to have minor bleeding than those treated in the hospital. A 2012 study determined that the outpatient treatment of patients with DVT utilizing LMWH is cost-effective and did not demonstrate any significant differences in the outcomes of patients.⁸² The in-patient treatment mean was \$4,338 and the mean outpatient cost was \$1,750.

For those patients whose home circumstances are determined to be adequate, initial treatment at home over treatment in the hospital is recommended by the ACCP guidelines (Grade 1B). Early ambulation is suggested over initial bed rest as well (Grade 2C). If edema and pain are severe, ambulation might need to be deferred, and then compression therapy is suggested.

Post-Thrombotic Syndrome

The PTS is a frequent complication of DVT. Patients complain of pain, swelling, heaviness, cramps, and itching or tingling of the affected leg. Ulcerations can occur. Standing and walking usually aggravate symptoms, whereas rest and elevation of the leg improve symptoms. Ipsilateral recurrent

venous thrombosis is strongly associated with subsequent development of moderate or severe post-thrombotic symptoms.⁸³ Therefore, prevention of recurrent thrombi likely reduces PTS. Utilization of a properly fitted compression stocking at the time of diagnosis and continued for at least 2 years can be effective in the reduction of post-thrombotic symptoms.⁸⁴ Stockings that are fitted to the patient with a specific pressure gradient may be prescribed.

The reported incidence of upper extremity PTS following UEDVT is 7–46%.^{31,85} The guidelines note no randomized trials evaluating compression bandages, compressive sleeves, or venoactive drugs to prevent PTS after UEDVT and thus suggest against the use of compression sleeves or venoactive medications for patients with acute symptomatic UEDVT (Grade 2C). However, they do mention anecdotal evidence that compression therapy benefits some patients with PTS of the arm, and the benefits of trialing compression therapy will outweigh the harm and cost. Thus, in patients who have PTS of the arm, a trial of compression bandages or sleeves is suggested to reduce symptoms (Grade 2C).

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Hyperglycemic Emergency

Grace S. Lee • Shyoko Honiden

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INTRODUCTION

Diabetic ketoacidosis (DKA) and hyperosmolar hyperglycemic state (HHS) encompass two severe complications of diabetes mellitus (DM). The incidence is steadily increasing in the United States despite efforts at prevention and education, with 140,000 hospitalizations for DKA in 2009, which was approximately a 75% increase over two decades.¹ Care has become more efficient, and the average length of stay (LOS) for DKA has decreased by about 2 days in the same period, with a mean time in the hospital of about 3.4 days in 2009.¹ In 2009, the hospital discharge rates for DKA per 1,000 individuals with diabetes were 32.4, 3.3, and 1.4 for people aged 44 and younger, for those between 45 and 64 years, and those aged 65 years and older, respectively.¹ Although the rate of hospitalizations for hyperglycemic crises continues to rise, mortality from DKA and HHS combined has been declining. In particular, mortality rates for those aged 75 years and older have precipitously declined in the last 2 decades (Figure 40-1). In 2009, there were 2,417 deaths caused by one of these two entities, which was nearly 20% lower than that in 1980.¹ In general, HHS has a lower rate of hospitalization but a higher mortality at a rate of 5% to 20%.^{2,3} The cost of DKA is profound and the aggregate cost of its hospitalizations is approximately \$850 million.⁴

DEFINITION OF DKA AND HHS

DKA is defined by the following criteria (Table 40-1): plasma glucose > 250 mg/dL, arterial pH ≤ 7.30, serum bicarbonate ≥ 18 mEq/L, presence of urinary and serum ketones, and

an anion gap > 10 mEq/L.² It is further divided into mild, moderate, and severe based on the degree of acidemia and serum bicarbonate level.² HHS is defined by the following criteria: plasma glucose > 600 mg/dL, an arterial pH > 7.30, serum bicarbonate > 18 mEq/L, an effective serum osmolality > 320 mOsm/kg (for which effective serum osmolality = 2 [measured Na⁺ (mEq/L)] + glucose [mg/dL]/18).^{2,5} Although HHS was previously called hyperglycemic hyperosmolar nonketotic state (HHNKS), small urinary and serum ketones may be seen in this condition; thus, their presence does not exclude the diagnosis of HHS.² In reality, DKA and HHS lie along a continuum; up to 33% of patients may have a clinical presentation in which features of both are present in varying degrees.³

Traditionally, DKA was thought to occur only in type 1 DM and HHS in type 2 DM. There is a newly recognized entity, however, of ketosis-prone type 2 DM.⁶ These patients present with DKA resulting from decreased insulin secretion and action, but they characteristically recover β -islet cell function within a few months.^{5,6} In long-term follow-up, up to 40% of these patients remain without exogenous insulin requirements 10 years after their initial presentation with DKA.⁵⁻⁷ Patients with ketosis-prone type 2 DM as a group tend to have obesity, family history of DM, lack of genetic HLA association, and low prevalence of autoimmune markers.⁶ There is a predilection for African, African American, and Hispanic patients—somewhere between 20% and 50% of patients with new-onset DKA in this demographic may fit this description—but cases have also been reported in other populations (Native American, Japanese, Chinese, white).⁶

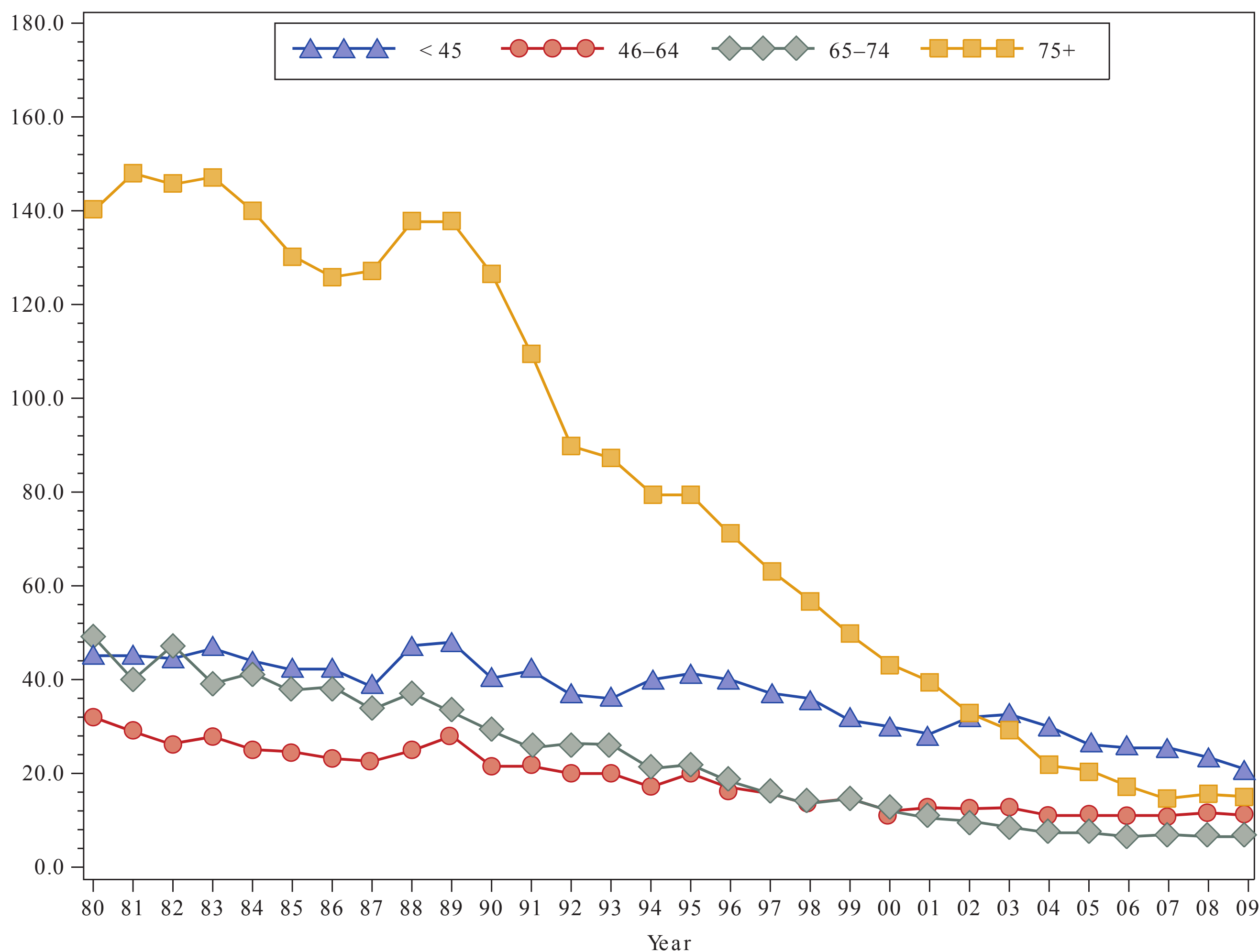


FIGURE 40-1 Death rates for hyperglycemic crises as underlying cause per 100,000 diabetic population, by age, United States, 1980–2009. Blue triangles represent the age group, including ages 44 years and younger. Red circles represent ages 45 to 64 years. Gray diamonds represent ages 65 to 74 years. Yellow squares represent ages 75 years and older. (Data from Division of Vital Statistics [National Vital Statistics System] and Division of Health Interview Statistics [National Health Interview Survey]. Available at <http://www.cdc.gov/diabetes/statistics/mortalitydka/fRateDKADiabByAge.htm>).

TABLE 40-1: Key Diagnostic Features of DKA and HHS			
	DKA		HHS
	Mild to Moderate	Severe	
Glycemia ^a	> 250 mg/dL		> 600 mg/dL
Arterial pH	7.00 to < 7.30	< 7.00	> 7.30
Serum bicarbonate (mEq/L)	10 to < 18	< 10	> 18
Ketonemia/ketonuria	Present	Present	Small
Serum osmolality	Usually < 320 mOsm/kg	Variable	> 320 mOsm/kg
Anion gap	> 10	> 12	Variable
Sensorium	Alert to drowsy	Stupor/coma	Stupor/coma

DKA = diabetic ketoacidosis; HHS = hyperosmolar hyperglycemic state.
^aRarely, patients may present with euglycemic ketoacidosis.

PATHOGENESIS OF DKA AND HHS

DKA is characterized by a state of relative insulin deficiency and concurrent increase in counterregulatory hormones (such as glucagon, cortisol, catecholamines, and growth hormone).^{2,5} Hyperglycemia occurs due to increased gluconeogenesis and glycogenolysis, and decreased peripheral glucose utilization in the liver, muscle, and adipocytes.⁵ Insulin deficiency and elevated cortisol levels lead to (a) increased proteolysis, which creates amino acid substrates that further fuel gluconeogenesis, and (b) increased lipolysis, which creates glycerol and free fatty acids (FFA).⁵ The latter undergo β -oxidation in the liver, which, in turn, generates ketone bodies, such as β -hydroxybutyrate and acetoacetate.⁵ Generation of these weakly acidic ketone bodies leads to the characteristic anion gap metabolic acidosis.⁵ Glycerol is used for further gluconeogenesis.⁵ Excess glucagon relative to insulin causes a decrease in malonyl CoA leading to the disinhibition of carnitine palmitoyl acyltransferase I (CPT I).⁸ CPT I facilitates ketogenesis by transporting FFA into the mitochondria for oxidation.⁸ Finally, as volume depletion causes prerenal azotemia, the ability to excrete glucose and ketoanions declines.⁹

In addition to the well-described metabolic disturbances outlined earlier, patients in states of hyperglycemic emergency also exhibit evidence of hypercoagulability and inflammation.^{8,10,11} Markers of coagulation, fibrinolysis, and platelet activity rise during DKA and may clinically manifest as thromboses, myocardial infarction (MI), and disseminated intravascular coagulation (DIC).^{8,10} In both DKA and HHS, a proinflammatory milieu develops as cytokines and other markers of cardiovascular risk and oxidative stress rise.¹¹

The pathophysiology of HHS, on the other hand, is not completely understood, but just as in DKA, osmotic diuresis leads to a loss of electrolytes and a free water deficit.³ The magnitude of total body water deficit is much greater in HHS and may exceed 9 L, whereas in DKA it typically ranges around 6 L.³ This leads to marked hyperosmolality, hypovolemia, and intravascular and extravascular dehydration, triggering an increase in counterregulatory hormones, which further worsens hyperglycemia and insulin resistance.^{5,8} In HHS, ketone production is minimal if not absent because enough insulin is present to suppress lipolysis.^{5,12}

DIAGNOSIS AND EVALUATION

Patients typically present with fatigue, weakness, polyuria, polydipsia, weight loss, and possibly altered mental status depending on the severity of presentation.² Additional history often present in DKA (but not HHS) includes generalized abdominal pain, nausea, and vomiting that tends to track the severity of acidemia.^{2,13} The pain may be of such severity that an acute abdomen is considered during the evaluation in 50% to 75%.^{5,13} The tempo of illness differs: DKA develops rather quickly within 24 hours, whereas HHS develops over a course of a few days to weeks.² In DKA, the physical exam may reveal tachycardia, hypotension, lethargy, dry mucous membranes, poor skin turgor, breath with fruity

odor (due to ketones), Kussmaul respirations, and abdominal tenderness.² Altered mental status, lethargy, and even coma are possible in both conditions, although they are more common in HHS due to the degree of hyperosmolality.^{3,14} In particular, obtundation and coma are typically seen when the effective osmolality is greater than 330 mOsm/kg.⁵ If the patient's osmolality is less than 320 mOsm/kg and obtundation is present, one must consider other etiologies for the altered mental status.^{2,5} In HHS, physical exam findings may include signs of dehydration as well as additional neurologic changes such as seizures or hemiparesis, making a thorough neurologic evaluation paramount.²

Initial evaluation should include an investigation for a precipitating factor. The most common precipitant for both DKA and HHS is infection.² Others include intentional or accidental insulin noncompliance, pancreatitis, cerebrovascular accident, MI, and medications (e.g., corticosteroids, diuretics, β -blockers, calcium channel blockers, cimetidine, diazoxide, phenytoin, sympathomimetic agents, pentamidine, typical or atypical antipsychotics).^{2,3,15} Elderly patients, in particular, have a greater risk of developing HHS due to poor thirst response and their dependence on others for free-water access.^{2,3} Other risk factors for DKA include psychological illness, eating disorders, and cocaine use.^{2,16} There are also some endocrine disorders that are associated with hyperglycemia: acromegaly, glucocorticoid excess, pheochromocytoma, thyrotoxicosis, and hyperaldosteronism.¹⁵ Some patients with Cushing's syndrome and DM may even develop HHS.¹⁵

Initial objective data should include an assessment of glycemia, readily obtained via fingerstick glucose, and a urinalysis to evaluate for ketones. It should be noted that, in some patients, the degree of hyperglycemia can be relatively mild (e.g., < 300 mg/dL) and even euglycemic DKA may be seen; thus, a higher index of suspicion is needed when an otherwise unexplained metabolic acidosis is seen. A detailed initial laboratory evaluation is outlined in Table 40-2. Of note, leukocytosis is typically seen in DKA with or without the presence of infection.² If the patient's white blood cell count is greater than $25 \times 10^3/\text{mm}^3$ or bandemia is 10% or greater, however, one should suspect a true infection.^{2,17} Nonspecific elevations in lipase and amylase, up to greater than three times normal values, may also be seen in up to 25% of patients with DKA; thus, one cannot diagnose acute pancreatitis by this laboratory value alone.¹⁸ An arterial blood gas (ABG) should be performed to determine the degree of acidemia.² In general, admission to the intensive care unit (ICU) is warranted if there is evidence of airway compromise, hemodynamic instability, severe acidemia, or any other finding that would suggest impending decompensation (e.g., suspected gastric dilation, acute abdomen).

Pseudohyponatremia may be present in the setting of hyperglycemia due to the shift of water to the extracellular space. For each 100 mg/dL of glucose greater than 100, 1.6 mEq/L must be added to the measured serum sodium level to arrive at the corrected sodium value.³ Although this is the traditional teaching, reevaluation of this correction factor showed that, for serum glucose greater than 400 mg/dL, a



TABLE 40-2: Initial Evaluation in DKA and HHS

Metabolic Evaluation	Infectious Evaluation	Imaging, Miscellaneous
Glucose	CBC with differential	Chest x-ray (CXR)
Urinalysis (for ketones)	Urinalysis	Electrocardiogram (ECG)
ABG	Urine culture	Abdominal plain film ^c
Electrolytes	Blood cultures	
• Sodium ^a	Viral nasal swab	
• Potassium		
• Chloride ^a		
• Bicarbonate ^a		
• Calcium		
• Magnesium		
• Phosphate		
Serum ketones		
Blood urea nitrogen (BUN)		
Creatinine		
Lactic acid		
Osmolarity		
Overdose panel ^b		
Urine toxicology panel ^b		
Liver function tests ^c		
Lipase ^c		

DKA = diabetic ketoacidosis; HHS = hyperosmolar hyperglycemic state.

^aUse to calculate the anion gap: AG = sodium – (chloride + bicarbonate).

^bTests to be considered if patient presents with recurrent DKA.^{14,16}

^cTests to be considered if abdominal pathology is suspected.

factor of 2.4 mEq/L was more appropriate, thus may be helpful in HHS.^{3,8}

The patient's serum potassium level may initially be elevated or near normal, which is falsely reassuring, as total body potassium levels are typically quite depleted.³ Insulin normally drives potassium into the intracellular space—as such, in the setting of absolute or relative insulin deficiency, potassium shifts to the extracellular space.⁹ Once treatment with insulin is initiated, the astute clinician must be prepared for a rapid decrease in the serum potassium level. Patients are at risk of developing cardiac arrhythmias and should be kept on telemetry.⁹

TREATMENT

The goals in the treatment of DKA and HHS are to treat the hypovolemia, free-water deficit, hyperglycemia, electrolyte abnormalities, and the precipitating factor, if one is present. In 2009, an ADA consensus statement proposed a revised treatment algorithm for DKA and HHS (Figure 40-2).² A recent retrospective study demonstrated that patients treated with a protocol based on this consensus statement had decreased time to resolution of DKA or HHS when compared to patients treated without a protocol.¹⁹ Both DKA and HHS require frequent monitoring of mental status, vital signs, and urine output. Laboratory monitoring may need to occur at 2- to 4-hour intervals until resolution.²

Initial treatment with intravenous fluids (IVF) is necessary in both DKA and HHS to replete the intravascular and interstitial spaces. Correction of hyperosmolarity has the added benefit of improving the patient's response to insulin.²⁰ First, normal saline (0.9% NaCl) should be given at a rate of 15 to 20 mL/kg body weight/h or 1 to 1.5 L over the first hour. At this point, based on the patient's hemodynamics, hydration status, serum sodium level, and urine output, the next composition of IVF is determined as outlined in Figure 40-2. If the patient remains hypotensive, isotonic fluids are continued. Insulin infusion is held until hemodynamic stability is achieved because, when insulin is given, water moves from the extracellular to the intracellular space, thus can worsen hypotension.⁸ Once the patient is normotensive, insulin infusion should begin at 0.1 U/kg/h. When determining the resuscitation rate, the patient's cardiac and renal functions are also taken into consideration. When the plasma glucose reaches 200 to 250 mg/dL in DKA (300 mg/dL in HHS), dextrose is added to the IVF to prevent hypoglycemia and insulin is continued at a lower rate, as ketoacidosis persists longer than hyperglycemia. It is important to continue insulin treatment well after resolution of hyperglycemia in order to suppress lipolysis and subsequent ketoacid production.

Regular intravenous (IV) insulin is typically used due to its relatively short half-life (5–17 minutes) and ease of administration. Studies have shown, however, that insulin therapy may be administered intravenously, subcutaneously,

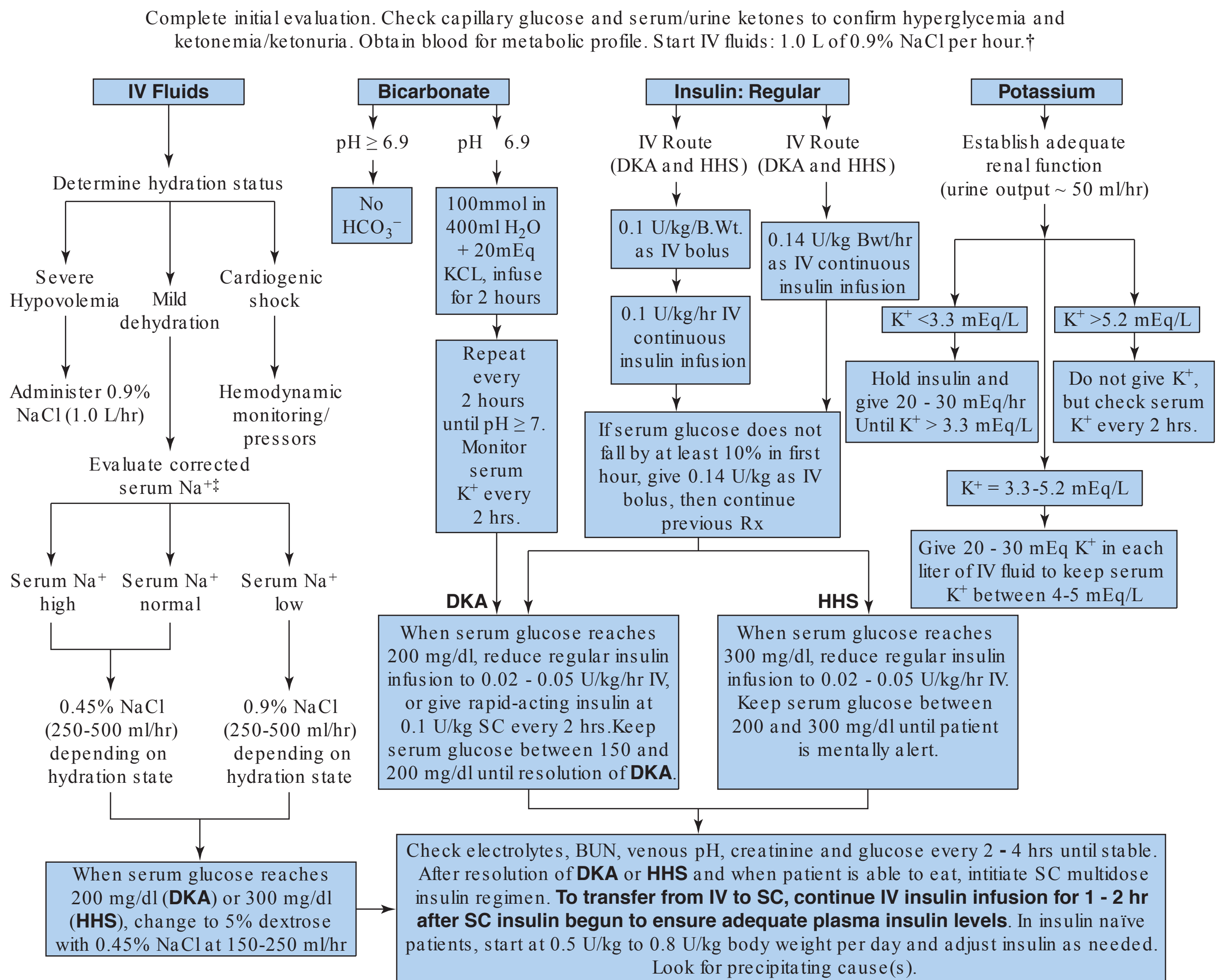


FIGURE 40-2 Management of adult patients with DKA or HHS. (Reproduced with permission from Kitabchi AE, et al: Hyperglycemic crises in adult patients with diabetes. *Diabetes Care*. Jul;32(7):1335–1343, 2009.)

or intramuscularly with good effect.²¹ In particular, treatment of mild and moderate DKA with rapid-acting insulin every 1 to 2 hours outside of the ICU has been demonstrated to be as effective as regular IV insulin therapy in the ICU.^{2,22} As for the use of bolus insulin, the traditional treatment protocol involves giving a 0.1 U/kg body weight bolus followed by a continuous infusion of 0.1 U/kg/h.² One study, however, demonstrated that an initial bolus of insulin is unnecessary if patients are given 0.14 U/kg body weight/h.²³ Another more recent prospective, observational cohort study showed that all outcomes examined were similar whether the patient received an initial bolus (at 0.1–0.15 U/kg) or not.²⁴ Thus, at this time, it appears that either method may be used to initiate treatment. In general, blood glucose should decline

at a steady rate of 50 to 75 mg/dL/h. Until this is achieved, the rate of the insulin infusion may be doubled every hour.²⁵

Given the expected decline in serum potassium level with the initiation of insulin therapy, insulin should be held if the patient's potassium is less than 3.3 mEq/L, as the intracellular shift of potassium triggered by insulin may further worsen hypokalemia and place the patient at risk for cardiac arrhythmias. The goal of potassium repletion is to maintain a level around 4 to 5 mEq/L. Repletion should begin when the level is at the upper limit of normal (5 mEq/L). Typically, adding 20 to 30 mEq/L of potassium to each liter of IVF will help prevent hypokalemia.² In one small prospective study of 26 patients treated for DKA, about two-thirds of patients developed hypokalemia with substantial repletion requirements, with an average of 145 mEq.²⁶

Patients with DKA also have total body phosphate depletion. However, studies have not convincingly shown benefit in aggressively repleting phosphate in these patients, and doing so may carry the risk of hypocalcemia.^{2,25,27} However, if serum phosphate levels are less than 1 mEq/L or if the patient has comorbid conditions—including respiratory depression, cardiac or respiratory compromise, or anemia—then repletion is warranted.^{2,25}

Resolution of DKA occurs when the blood glucose is < 200 mg/dL and two of the following occur: serum bicarbonate level \geq 15 mEq/L, venous pH > 7.3, and/or anion gap \leq 12 mEq/L. Resolution of HHS occurs when the osmolality and mental status have normalized. At this time, subcutaneous insulin may be initiated with at least 1 to 2 hours of overlap with the insulin infusion to prevent relapse. Regarding the dose of subcutaneous insulin, the patient's home insulin regimen may be used if it had been working well for the patient prior to the episode. In newly diagnosed diabetic patients, dosing should start at 0.5 to 0.8 U/kg per day. The total daily dose should be divided into a basal and bolus regimen. One approach is to allocate 50% of the total daily dose as long-acting insulin, such as glargine, and to divide the remainder into three equal mealtime boluses of rapid-acting insulin (e.g., aspart or lispro).²

Bicarbonate therapy is controversial in the treatment of DKA. As DKA is treated, ketoacidosis should improve because ketone bodies are metabolized in the citric acid cycle.⁸ This leads to the production of carbon dioxide and water, which leads to regeneration of bicarbonate.⁸ Studies have failed to demonstrate that bicarbonate therapy has any benefit in improving morbidity or mortality in patients with severe DKA (pH 6.9–7.1).^{2,28} There are no randomized controlled trials, however, that have examined the role of bicarbonate therapy in DKA patients with a pH < 6.9.⁹ In severe acidemia, patients are at risk for developing cerebral vasodilatation, coma, decreased myocardial contractility, and gastrointestinal (GI) complications.^{2,29} Given these risks, the current recommendation is to give bicarbonate therapy to DKA patients with a pH < 6.9. It is important to note that bicarbonate therapy carries the risks of worsening hypokalemia, worsened intracellular acidosis, cerebral edema, and paradoxical central nervous system acidosis.² See Figure 40-1 for dosing.

COMPLICATIONS

Potential complications during treatment of DKA and HHS include cerebral edema, hypoglycemia, hypokalemia, hyperchloremic metabolic acidosis, fluid overload, acute respiratory distress syndrome (ARDS), thromboembolism, and acute gastric dilation due to gastroparesis.^{2,3,8,30}

Cerebral edema is rarely seen in adult patients with DKA; the exact mechanism of cerebral edema is not entirely clear. Most of the literature is in the pediatric population. There is evidence to support the following theories: inflammatory mediators, cerebral ischemia, hypoxia, and rapid decline in serum osmolality due to aggressive IVF.² If present, patients may develop a headache, altered level of consciousness, papilledema,

bradycardia, hypertension, seizures, incontinence, or even respiratory arrest.^{2,3,30} Treatment includes giving mannitol and mechanically ventilating the patient.³⁰

A more common complication is development of hyperchloremic nonanion gap metabolic acidosis resulting from large amounts of normal saline given during treatment and the decrease in ketoanions as DKA resolves.⁹ In addition, fluid overload or ARDS could also occur; thus, frequent cardiopulmonary assessment is vital.⁹ Given the possibility of gastroparesis and resulting gastric dilation, serial abdominal exams and an abdominal plain film should take place if there are sufficient clinical concerns.⁸

SUMMARY

DKA and HHS lie along a continual spectrum, and are frequently encountered diabetic complications in the acute care setting, with significant economic burden and morbidity for the patient. With prompt diagnosis and careful management, DKA and HHS can be successfully managed, with improved patient outcomes.

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Glucose Management in Critical Care

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INTRODUCTION

The American Diabetes Association (ADA) defines inpatient hyperglycemia as a fasting blood glucose (BG) > 126 mg/dL or a random BG > 200 mg/dL that reverts to normal after discharge.¹ The prevalence of hyperglycemia in the acutely ill patient in the intensive care unit (ICU) has been shown to be as high as 83%.² Hyperglycemia in critical illness may occur due to stress-related surges in counterregulatory hormones, preexisting diabetes, impaired glucose tolerance, and insulin resistance. Whether it is a condition necessitating intervention or a marker of disease severity, hyperglycemia has been shown to be an independent risk factor for increased mortality in the ICU.³ Despite this association, tight glycemic control (TGC) has not been shown to consistently improve patient outcomes and, surprisingly, may cause more harm than good in some subgroups. This chapter examines the historical background, essential pathogenesis, associations, key clinical studies, current protocols, and recommendations regarding hyperglycemia in the critically ill.

HISTORICAL BACKGROUND

Hyperglycemia was first detected as glucosuria in ether-anesthetized patients 150 years ago. In 1877, Bernard described hyperglycemia in a canine model of hemorrhagic shock.⁴ For

many years, hyperglycemia in the critically ill was considered an adaptation to stress and was not treated. In fact, some early ICU practitioners recognized insulin resistance and believed that elevated glucose levels (160–200 mg/dL) would promote cellular glucose uptake. In 2001, Van den Berghe demonstrated a statistically significant mortality benefit with TGC in surgical ICU patients.⁴ Subsequently, many professional societies, including the Surviving Sepsis Campaign (SSC), endorsed TGC in 2004.⁵ The Leuven (Van den Berghe et al.) medical trial in 2006,⁶ VISEP (Efficacy of Volume Substitution and Insulin Therapy in Severe Sepsis, Brunkhorst et al.) trial in 2008,⁷ and NICE-SUGAR (Normoglycemia in Intensive Care Evaluation—Survival Using Glucose Algorithm Regulation, Finfer et al.)⁸ and Glucontrol (Preiser et al.)⁹ trials published in 2009 have contributed most to the continuously evolving issue of glucose management in the critically ill patient.

PATHOGENESIS OF HYPERGLYCEMIA IN ICU SETTING

Risk factors for the development of hyperglycemia include preexisting diabetes mellitus, advanced age, infusion of catecholamine pressors, glucocorticoids, obesity, excessive dextrose resuscitation, sepsis, hypothermia, hypoxia, uremia, and cirrhosis.¹⁰ These proven risk factors highlight the multifactorial pathogenetic mechanisms underlying ICU hyperglycemia.

In the critically ill patient, hyperglycemia can be explained by increased glucose production (glycogenolysis and gluconeogenesis) and decreased peripheral uptake (insulin resistance; Figure 41-1).

Increased glucose production: Counterregulatory hormones and catecholamines—such as glucagon, growth hormone, cortisol, and epinephrine—increase adipose tissue lipolysis and skeletal muscle proteolysis. The endproducts from this process (glycerol, alanine, and lactate) then fuel hepatic gluconeogenesis. By directly enhancing hepatic glycogenolysis, these hormones simultaneously further raise glucose levels. Impairment of cellular glycogen synthesis is another important pathway leading to increased glucose levels.

Decreased peripheral uptake: In a healthy subject, insulin binds to its receptor, triggering a signaling pathway that ultimately leads to the translocation of the intracellular Glut4 protein to the plasma membrane, where

it is responsible for glucose uptake. Although not well understood, it has been postulated that critical illness inhibits Glut4 translocation, resulting in hyperglycemia. Counterregulatory hormones and cytokines are believed to play an important role in this process.

Insulin resistance—defined as ongoing gluconeogenesis, glycogenolysis, lipolysis, and proteolysis despite normal or elevated insulin levels—is directly or indirectly (via counterregulatory hormones) modulated by proinflammatory cytokines, such as tumor necrosis factor (TNF)-alpha, interleukin (IL)-1, and IL-6.

ASSOCIATION OF HYPERGLYCEMIA AND POOR OUTCOME

Even prior to the seminal randomized control trial (RCT) by Van den Berghe in 2001, which showed a statistically significant 30% excess mortality, there have been numerous

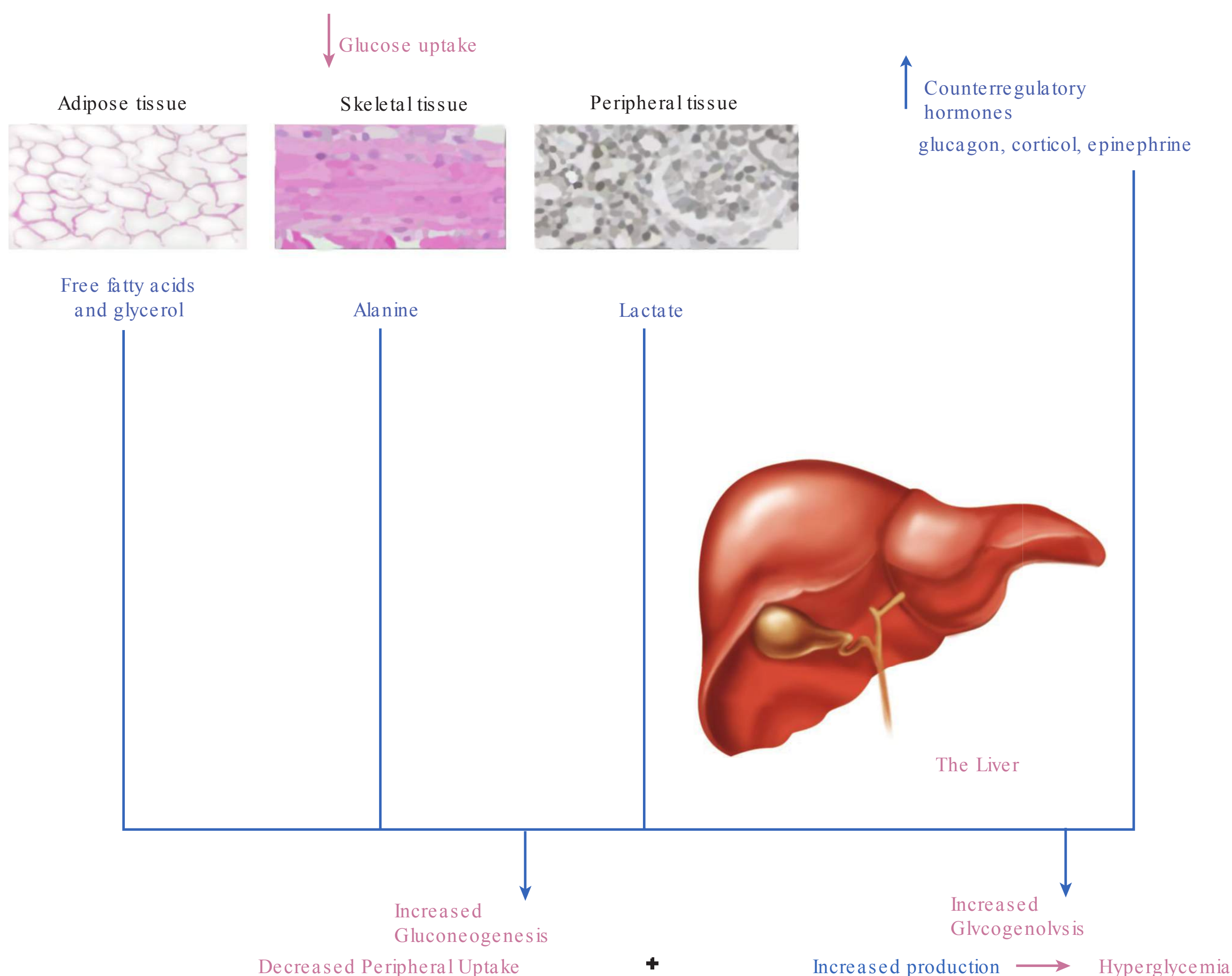


FIGURE 41-1 Effect of critical illness on glucose metabolism. Critical illness leads to decreased glucose uptake in adipose, skeletal, and peripheral tissue despite normal or high insulin levels, so-called insulin resistance. Counterregulatory hormones stimulate lipolysis, proteolysis, and glycolysis. The endproducts glycerol, alanine, and lactate are then used in the liver for gluconeogenesis. The simultaneous hormone-induced glycogenolysis further contributes to the ensuing hyperglycemic state.

retrospective studies showing a strong association between poor ICU-related outcomes in hyperglycemic patients.¹¹ For instance, Sung et al. demonstrated that admission hyperglycemia in trauma patients was an independent risk factor for increased mortality, ICU length of stay (LOS), and infection.¹² In traumatic brain injury patients, Young et al. showed significantly worse 3-month and 1-year outcomes if the blood glucose levels were > 200 mg/dL.¹³ In patients with ischemic and hemorrhagic stroke, Weir et al. demonstrated that a plasma glucose concentration above 144 mg/dL predicted poorer chances of survival and functional independence, even after adjusting for age and stroke severity.¹⁴

Similar results have been found in retrospective studies, which focused on a heterogeneous population of ICU patients. Most notably, Krinsley studied 1,826 consecutive ICU patients (roughly 80% medical and 20% surgical) and found that hospital mortality increased progressively as glucose values increased, reaching 43% among patients with mean glucose values exceeding 300 mg/dL.³

Among surgical patients, one of the key mechanisms by which insulin may improve outcomes is through reduction in infections. Studies supporting such a connection have demonstrated a three-fold increased risk of postoperative wound infections and a four-fold increased incidence of intravascular infections in hyperglycemic surgical ICU patients.^{5,10}

KEY TRIALS OF HYPERGLYCEMIC CONTROL IN ICU POPULATION

Initial enthusiasm for intensive insulin therapy (IIT) stimulated by the initial Leuven surgical trial was dampened by the subsequent 4 RCTs that not only failed to show clear mortality benefits but further highlighted the possible dangerous consequences of IIT.

Subgroup analysis of the initial Leuven surgical trial showed that the greatest mortality benefit was achieved in patients who had a prolonged ICU stay of > 5 days.¹⁵ Consequently, the Leuven medical trial specifically targeted patients with prolonged (> 3 days) ICU stay. Although demonstrating a mortality benefit in that subgroup once again, the intention-to-treat design failed to demonstrate a mortality benefit of IIT in overall patients and is widely considered a negative trial despite the listed morbidity benefits in all subgroups.⁶

The purpose of the VISEP trial was to determine if the benefit of strict glucose control applied to patients with severe sepsis and septic shock. Due to unacceptably high hypoglycemia rates, the VISEP trial was prematurely terminated and did not reach the recruitment goal. The trial's subsequent lack of power coupled with potential confounding agents inherent in the four-arm design may explain why this trial also failed to show an IIT benefit for both mortality and morbidity.⁷

Anoteworthy point of the negative Glucontrol trial was the lower BG target levels (140–180 mg/dL vs. 180–200 mg/dL) in the conventional arm. Although terminated early for protocol violations and failure to reach target BG levels, those IIT patients who did reach target levels still did not have a mortality benefit when compared with the conventional arm.⁹

The largest and perhaps most definitive trial to date, NICE-SUGAR, showed a significantly *increased* mortality rate in the IIT group at 90 days and no positive effect on morbidity as well. For reasons that are not yet clear, excess deaths were predominantly due to cardiovascular causes. Interestingly, despite worse mortality, there were no observable differences in ICU or hospital LOS, new-organ failure rates, ventilator days, bacteremia, or transfusion requirements between the two groups. Also noteworthy is that roughly 33% of the NICE-SUGAR patients were surgical and, unlike the original Leuven surgical trial, there was no mortality benefit in this subgroup.⁸

Finally, a recent RCT from France, the CGAO-REA study, investigated whether a computer decision support system might improve the outcome of ICU patients through facilitating tighter BG control. The largest RCT in the field of glucose control in the ICU after the NICE-SUGAR trial, this study showed no significant difference between the tight computerized glucose control group (BG target of 4.4–6.1 mmol/L) versus the conventional noncomputerized glucose control group (BG target < 10 mmol/L).¹⁶ It is worth highlighting that the mortality was not worse in the TGC group despite having a twofold higher incidence of moderate and severe hypoglycemic episodes.

A concise summary of the key trials highlighting the study population, endpoints, adverse effects and criticisms can be found in Table 41-1.

SELECTED SUBGROUP POPULATIONS

In addition to the aforementioned key RCTs, TGC has also been studied in patients with acute myocardial infarctions (MIs), coronary artery bypass grafts (CABGs) and cerebral vascular accidents (CVAs).

MI and Post-CABG Patients

Hyperglycemia has been shown to be a risk factor for mortality in patients with acute MI. In a study of 16,781 patients with acute MI, the mortality rate increased incrementally with each 10 mg/dL rise in glucose over 120 mg/dL.¹⁷ Studies have shown that hyperglycemia in the presence of ischemia is associated with decreased collateral circulation, increased infarct size, and prolonged QT interval.¹⁸ Since hyperglycemia has been clearly linked to less Thrombolysis In Myocardial Infarction (TIMI) flow before primary percutaneous coronary intervention (PCI), it has been hypothesized to be a strong prothrombotic stimulus initiating procoagulant factors and inhibiting thrombolysis.¹⁹ In addition to counteracting these deleterious procoagulant effects, insulin blocks the accumulation of free fatty acids generated from ischemia-induced myocardial anaerobic metabolism that otherwise would promote further oxygen debt and arrhythmias.²⁰

Initial enthusiasm was sparked by the DIGAMI (Diabetes and Insulin-Glucose infusion in Acute Myocardial Infarction) trial, an RCT that studied diabetics with acute MI. An impressive 30% mortality reduction was shown in the glucose,



TABLE 41-1: Review of Prospective Randomized Trials of Glycemic Control Among Critically Ill Patients^{11–16}

Year	Population # Patients Centers	Goal Glucose Level	Primary Outcome and Endpoints	Adverse Effects	Key Findings and Comments	Key Criticisms
1991	Surgical ICU 1548 Single Site	<u>TGC</u> 80–110 mg/dL <u>Conventional</u> 180–200 mg/dL	<u>ICU Mortality</u> TGC: 4.6% Conv: 8% P < 0.04	<u>Hypoglycemia</u> TGC: 5% Conv: 0.7%	TGC reduced mortality during ICU/hospital stay, morbidity, renal failure, hyperbilirubinemia, bloodstream infection, duration of mechanical ventilation, and ICU/hospital stay	Use of parenteral nutrition to achieve caloric goals in both groups. High mortality rates in the control group (8%).
2006	Medical ICU 1200 Single Site	<u>TGC</u> 80–110 mg/dL <u>Conventional</u> 180–215 mg/dL	<u>In-Hospital Mortality</u> TGC: 37.3% Conv: 40.0% P = 0.33	<u>Hypoglycemia</u> TGC: 18.7% Conv: 3.1%	<u>≤ 3-day ICU stay</u> TGC—No significant difference in mortality. Decreased duration of mechanical ventilation, ICU and hospital length of stay <u>≤ 3-day ICU stay</u> TGC—Decreased mortality in hospital and at 90 days, duration of mechanical ventilation, ICU and hospital length of stay	Subjective inclusion criteria (ICU length of stay < 3 days). Unusually high rates of hypoglycemia in TGC group.
2008	Medical and Surgical ICU *** only with pts with severe sepsis/shock 537 18 sites	<u>TGC</u> 80–110 mg/dL <u>Conventional</u> 180–200 mg/dL	<u>28-day Mortality</u> TGC: 24.7% Conv: 26% P = 0.74	<u>Hypoglycemia</u> TGC: 17% Conv: 4.1%	Stopped early for safety concerns due to large number of hypoglycemic episodes in TGC. Before trial was stopped, there was no difference in mortality at 28 and 90 days.	Large number of hypoglycemic episodes in TGC group.
2006	Medical and Surgical ICU 1101 21 sites	<u>TGC</u> 110–140 mg/dL <u>Conventional</u> 140–180 mg/dL	<u>ICU Mortality</u> TGC: 17.2% Conv: 15.3% P = 0.41	<u>Hypoglycemia</u> TGC: 8.7% Conv: 2.7%	Trial was terminated early after the first interim analysis due to failure to achieve targeted blood glucose levels and high rates of hypoglycemia.	Failure to achieve targeted blood glucose levels. High rates of hypoglycemia.
2009	Medical and Surgical ICU 6104 42 sites	<u>TGC</u> 81–108 mg/dL <u>Conventional</u> < 180mg/dL	<u>90-day Mortality</u> TGC 27.5% Conv 24.9% P = 0.02	<u>Hypoglycemia</u> TGC: 6.8% Conv: 0.5%	TGC—Increased mortality at 90 days. No difference between groups in need for dialysis, duration of mechanical ventilation, or days in ICU/hospital	Subjective inclusion criteria (ICU length of stay > 3 days). Achievement of glucose levels modestly above target range in large portion of TGC group.
2014	Medical and Surgical ICU 2684 34 sites	<u>TGC</u> 4.4–6.1 mmol/L <u>Conventional</u> < 10 mmol/L	<u>90-day Mortality</u> TGC: 32.3% Conv: 34.1% P = 0.32	<u>Hypoglycemia</u> < 2.2 mmol/L TGC: 13.2% Conv: 6.2%	TGC—No significant difference from conventional in 90-day mortality <i>despite</i> more frequent severe hypoglycemia	Subjective inclusion criteria (ICU length of stay > 3 days). BG levels were lower than expected in the control group → lower difference in levels between the groups. Conventional group had very high severe hypoglycemia rate.

Tight Glucose Control; Conv = Conventional Control.



insulin, and potassium (GIK) infusion group.²¹ However, the larger and more recent 2005 follow-up study, DIGAMI-2, did not replicate such findings.²² Similarly, the CREATE-ECLA trial showed no difference in mortality, cardiac arrest, or cardiogenic shock in ST-elevation MI (STEMI) patients randomized to a GIK infusion.²³ Although the subsequent HI-5 study in 2006 also did not show a mortality benefit in diabetic acute MI patients randomized to GIK, there was a significantly lower incidence of heart failure and reinfarction in that group, which has revived the pro-IIT debate.²⁴

It is worth noting that, unlike the TGC studies such as NICE-SUGAR and the Leuven trials, the GIK infusion acute MI studies, such as the CREATE-ECLA and DIGAMI trials, did not really achieve TGC. Ostensibly, these trials focused more on insulin therapy than on the control of hyperglycemia.

Hyperglycemia is a known risk factor for mortality, deep sternal wound infections, and increased LOS in patients undergoing CABG. The ongoing large Portland Diabetic Project, which is a prospective, nonrandomized, observational study including 5,510 diabetic patients, has shown a dramatic and significant 60% to 77% decrease in mortality and infection risk when employing a continuous insulin infusion.²⁵

CVA Patients

Patients with acute stroke (cerebrovascular accident [CVA]) have been shown to have worse outcomes when hyperglycemic. The detrimental effects of hyperglycemia may include increasing tissue acidosis secondary to anaerobic glycolysis, lactic acidosis, and free radical production along with a possible contribution to cerebral edema via an effect on the blood-brain barrier.²⁶ There is a recognized three-fold increase in hemorrhagic transformation in tissue plasminogen activator (tPA)-treated hyperglycemic post-CVA patients as well. A 2001 comprehensive cohort review demonstrated a three-fold increase in 30-day mortality among hyperglycemic post-CVA patients.²⁷ While admission BG > 140 mg/dL has significant long-term mortality association, Baird found that persistent hyperglycemia (BG > 200 mg/dL) during the first 24 hours after stroke independently predicted expansion of the volume of ischemic stroke and poor neurologic outcomes.²⁸ A 2009 large observational Glycemia in Acute Stroke (GLIAS) study showed that a BG > 155 mg/dL or higher at any time within the first 48 hours from stroke onset was associated with poor outcome independently of stroke severity, infarct volume, diabetes, or age.²⁹

To date, few RCTs studying BG control in the post-CVA patient have been published. One such RCT, the GIST-UK trial in 2008, did not show a mortality or morbidity effect of IIT in acute CVA patients, but was underpowered and the length of treatment (24 hours) was minimal.³⁰ Additionally, the IIT group in the GIST-UK trial only had a mean BG level of 10.3 mg/dL lower than the control group. Since it was suggested that greater reductions in BG levels might be needed to show a clinical benefit, 2 recent RCTs focused on the clinical feasibility and safety of more aggressive intensive insulin protocols. These studies, which focused on patients

with preexisting diabetes, suggested clinical benefit, but were unable to demonstrate definitive improvement.^{31,32} Of importance, the aforementioned prospective RCTs excluded nondiabetics because they tend to self-correct and enter the target range without intervention.

Given the paucity of RCTs, the guidelines for BG control in CVA patients vary and are constantly evolving. The European Stroke Organization guidelines recommend starting insulin therapy when the BG is > 10 mmol/L (181 mg/dL).³³ The Stroke Council of the American Stroke Association, which in 2003 initially recommended BG control only when the BG is > 300 mg/dL, has recently changed the BG target to 140 to 185 mg/dL (7.7 to 10.2 mmol/L).³⁴

For a detailed summary of the MI and CVA studies, see Table 41-2.

RISKS OF HYPOGLYCEMIA IN THE ICU

The Leuven surgical and medical, NICE-SUGAR, VISEP, and Glucontrol trials, as well as the aforementioned RCTs in selected subgroup populations, have all shown a risk of hypoglycemia in the intensive glucose control groups. Symptoms of hypoglycemia—such as headache, fatigue, confusion, and dysarthria—are often masked in an ICU patient and may not become evident until the BG is < 40 mg/dL. Complications of such severe hypoglycemia include coma, seizures, and even cardiac arrest. In 2007, Krinsley identified severe hypoglycemia in ICU patients as an independent risk factor for mortality. In fact, a single episode of severe hypoglycemia was shown to significantly increase the risk of mortality over two-fold. The populations at greatest risk of mortality secondary to hypoglycemia were the patients with preexisting diabetes, on mechanical ventilation, with an admitting diagnosis of septic shock, and with a very high Acute Physiology and Chronic Health Evaluation (APACHE) score.³⁵ A post-hoc observational analysis of the NICE-SUGAR trial found that moderate (41–70 mg/dl) and severe hyperglycemia (≤ 40 mg/dl) are strongly associated with an increased risk of death in critically ill patients, especially in patients with distributive shock.³⁶ It has been suggested that the mortality benefit provided with IIT can perhaps be offset if IIT is too intense; thus, finding the right balance is of utmost importance. It is worth noting that point of care glucose monitoring (POCT) usually directs the insulin dose in most ICUs and tends to overestimate (perhaps mostly in anemic, hyperoxic, or hypoxic patients) blood sugar concentration.^{37,38} Thus, the risk of undetected hypoglycemia, especially in an intense glucose control population, should be considered.

TREATMENT AND RECOMMENDATIONS

In review, although it is clear that severe hyperglycemia is associated with poor outcomes, there is no convincing data to suggest that the tightest glucose control (80–110 mg/dL)



TABLE 41-2: Review of Prospective Randomized Trials of Glycemic Control Among MI and CVA Patients^{21–24,30}

Year	Population # Patients Centers	Goal Glucose Level	Intervention	Primary Outcome and Endpoints	Key Findings and Comments	Key Criticisms
MI 1999	MI patients with admission glucose > 198 mg/dL 620 19 sites	<u>TGC</u> 126–180 mg/dL <u>Conv</u> Physician discretion	<u>TGC</u> Insulin and glucose infusion for > 24 hours, then SQ insulin for 3 months. <u>Conv</u> Glucose control at the discretion of treating physician.	<u>Mortality during average follow-up of 1.6–5.6 years</u> TGC: 33% Conv: 44% P = 0.011	Improved mortality in the TGC group	Inconsistent glucose control in the Conv group due to physician discretion and no goal glucose level.
MI 2005 RAD	MI patients with admission glucose > 198 mg/dL 1253 48 sites	<u>TGC (1 and 2)</u> Fasting 126–180 mg/dL <u>Conv</u> Physician discretion	<u>TGC (1)</u> 24-hour insulin and glucose infusion, followed by long-term SQ insulin. <u>TGC (2)</u> 24-hour insulin and glucose infusion followed by glucose control at the discretion of treating physician. <u>Conv</u> Glucose control at the discretion of treating physician.	<u>2-year Mortality</u> TGC(1): 23.4% TGC(2): 21.2% Conv(3): 17.9% P value 1:2 = 0.832 1:3 = 0.157 2:3 = 0.203	No difference in mortality or morbidity between the three groups.	Inconsistent glucose control in the Conv group due to physician discretion and no goal glucose level. 14% of Conv group received insulin and glucose infusion as per the treating physician. Significant differences in the patient characteristics of the 3 groups. Study was stopped early due to slow recruitment rates.
TE-LA 2005	STEMI patients 20,201 470 sites	No set glucose goals	<u>Test Group</u> Glucose Insulin Potassium (GIK) infusion—infused over 24 hours after admission, along with 7 days of low-molecular weight heparin reviparin. <u>Control</u> Usual care	<u>30-day Mortality</u> GIK: 10% Cont: 9.7% P = 0.45	No difference in mortality, cardiogenic shock, or cardiac arrest in patients s/p STEMI.	No correlation with previous smaller studies involving GIK infusion. Test group had glucose infusion as part of insulin drip which may have led to negative results.



6	MI patients with admission blood glucose > 140 mg/dL 240 6 sites	<u>TGC</u> 72–180 mg/dL <u>Conv</u> No set glucose goals	<u>TGC</u> Insulin and dextrose infusion for at least 24 hours after admission. <u>Conv</u> Patients remained on their usual diabetes therapy, including SQ insulin. Metformin was discontinued on admission. If blood glucose > 288 mg/dL, SQ insulin was permitted.	<u>Inpatient Mortality</u> TGC: 4.8% Conv: 3.5% P = 0.75 <u>3-month Mortality</u> TGC: 7.1% Conv: 4.4% P = 0.42 <u>6-month Mortality</u> TGC: 7.9% Conv: 6.1% P = 0.62	No difference in mortality. <u>TGC</u> Lower incidence of cardiac failure and evidence of reinfarction at 3 months.	Significant difference in blood glucose between TGC and Conv group was not achieved. Mean duration of time from symptoms to infusion initiation in TGC group was 13 hours.
UK 7	Acute stroke patients Excluding patients with h/o IDDM and hyperglycemia on presentation > 17 mmol/dL (306 mg/dL) 933 Multicenter	<u>Glucose Potassium and Insulin Infusion (GIK)</u> 72–126 mg/dL <u>Control</u> No set glucose goals. If glucose > 306 mg/dL, insulin infusion could be started based on physician_discretion.	<u>GIK</u> Glucose, insulin, and potassium infusion for at least 24 hours after admission. <u>Control</u> 0.9% Saline infusion at 100 mL/hour	<u>90-day mortality</u> GIK: 30% Control: 27.3% P = 0.37	No difference in mortality. <u>GIK</u> Reduced mean serum glucose levels by 10 mg/dL and blood pressure by 9 mm Hg	Trial was stopped early due to slow enrollment. Most patients had only moderate elevations in plasma glucose on admission and patients with severely high serum glucose (> 306 mg/dL) were excluded from the study. GIK infusion was labor intensive and had a 15.7% incidence of hypoglycemia requiring rescue treatment.

Tight Glucose Control; Conv= Conventional Treatment; Cont = Control; MI = Myocardial Infarction; STEMI = ST Elevation Myocardial Infarction; IDDM = Insulin Dependent Diabetes Mellitus.

provides mortality benefits. An early single-center surgical study showing morbidity and mortality improvements rushed in an era of intensive insulin protocols around the world. Subsequent studies, however, including medical patients and a more heterogeneous group of ICU patients, have failed to replicate this finding.

The updated Surviving Sepsis Campaign (SSC) guidelines recommended that patients with severe sepsis and hyperglycemia should be placed on intravenous insulin infusion to reduce BG levels with a goal of < 150 mg/dL.³⁹ In June 2009, an addendum published by the SSC glucose control subgroup in response to the NICE-SUGAR publication recommended against IIT aimed at BG 80–110 mg/dL in patients with severe sepsis. They did, however, recommend considering glucose control when levels exceed 180 mg/dL, with a goal BG approximating 150 mg/dL.⁴⁰ In 2009, the ADA and American Association of Clinical Endocrinologists (AACE) guidelines advocated a BG target of 140–180 mg/dL with initiation of insulin therapy when BG is > 180 mg/dL.⁴¹ This has remained the consensus statement recently updated in 2014.¹

Glycemic control in the ICU can be obtained by either intravenous (IV) and/or subcutaneous (SQ) insulin. In a systematic literature review by Meijering in 2006, the IV route achieved a target BG level in a higher number of patients than the SQ route alone.⁴² The standard of care in the ICU is to use IV infusions when feasible and not SQ and IV together.

There are at least 18 current insulin protocols available, but the concept is the same: achieve the best BG control while minimizing the risk of hypoglycemia.⁴³ A typical “sliding” protocol, as seen in the Leuven surgical trial, sets a predetermined amount of insulin according to the range in which the last BG value fell. On the other hand, “dynamic” protocols, such as Goldberg’s Yale protocol, make adjustments based on glycemic levels, as well as the rate of change and the degree of insulin resistance.

In transitioning from the ICU to general or intermediate care within the hospital, BG control is still targeted, albeit less tightly. The use of a basal-bolus regimen (i.e., adding basal coverage in addition to the sliding scale dose) has been shown to be almost two times more effective at achieving target BG levels in non-ICU patients than the traditional sliding scale protocols alone.⁴⁴

THE FUTURE OF ICU HYPERGLYCEMIC CONTROL

The contemporary ICU and hyperglycemic control debate has recently focused on whether such patients are diabetic or not. For instance, Egi et al. showed in a retrospective study that nondiabetic patients in their ICU with glucose levels 180 to 198 mg/dL were 3.3 times more likely to die in the ICU than the diabetic patients with the same glucose range.⁴⁵ Krinsley et al. discovered a roughly five-fold higher mortality rate among nondiabetic patients with mean glucose levels ≥ 180 mg/dL compared to those with mean glucose levels 70 to 99 mg/dL; the diabetic patients with mean

glucose levels ≥ 180 only exhibited a doubling of the mortality rate in comparison.⁴⁶ Perhaps most strongly making this point that a single glucose target does not appear optimal for all critically ill patients, a recent large retrospective cohort by Lanspa et al. found a greater mortality with moderate glucose control (90–140 mg/dL) compared to tight glucose control (80–110 mg/dL) in critically ill nondiabetic patients.⁴⁷ Upcoming RCTs will likely separate diabetic and nondiabetic ICU patients for analysis.

Current and future studies focus on incorporating some new approaches evaluating metrics of hyperglycemia beyond average values, such as glycemic variability. Interesting ongoing studies with the goal of avoiding or reducing insulin use focus on utilizing insulin-like growth factor-1 (IGF-1, a signal in the insulin pathway), glucagon-like peptide-1 (GLP-1, a glucose-lowering incretin) or even simply restricting carbohydrates.⁴⁸ Providing better and safer target BG levels, further improving protocol adherence via online and computerized tools, and incorporating advanced continuous glucose monitoring devices through indwelling venous or arterial catheters are also exciting subjects for future investigation, and are likely to contribute to the evolution of glycemic control in the ICU population.

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Adrenal Insufficiency

Evie G. Marcolini • William C. Chiu

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BACKGROUND

Adrenal gland function has provided great academic material for investigation and controversy. It was not until 1937 that 17-hydroxy-11-dehydrocorticosterone, or cortisone, was isolated by Reichstein from the adrenal cortex. By 1947, synthetic cortisone was developed. At the same time, in addition to the use of cortisone for Addison disease, this compound was found to have a therapeutic effect in patients with rheumatoid pain through its ability to inhibit stress and inflammation.

Adrenal insufficiency presents as chronic primary (about 5 per million incidence) or secondary (about 200 per million incidence). Both of these entities are more common in women, and diagnosis peaks anywhere from the fourth to the sixth decade. Historically, the most common cause of adrenal insufficiency was tuberculous adrenalitis. In developed countries, autoimmune adrenalitis has become a much more common cause of adrenal insufficiency, as tuberculous adrenalitis still plays a major role in the disease in developing countries.¹

The adrenal gland has two anatomic divisions. The medulla secretes the catecholamines epinephrine and norepinephrine, and the cortex produces mineralocorticoids (via the renin–angiotensin system) and glucocorticoids. Critical illness and stress activate the hypothalamic–pituitary–adrenal (HPA) axis and stimulate the release of hypothalamic corticotropin-releasing hormone (CRH) and pituitary adrenocorticotrophic hormone (ACTH).² ACTH secretion reaches its effector organ, the adrenal cortex, where it stimulates the synthesis and secretion of glucocorticoids, mineralocorticoids, and adrenal androgens. The mechanisms regulating ACTH secretion during stress are multifactorial, with the stimulatory effect of CRH and the inhibitory influence of cortisol. The “closed-loop” negative feedback of cortisol to the HPA axis acts to suppress the secretion of CRH, ACTH, and cortisol itself (Figure 42-1).

Physiologic ACTH and cortisol secretion have a diurnal pattern, with nadirs at 10 pm and 2 am, and peak at 8 am. During infection and inflammatory states, cortisol levels are increased through stimulation of the hypothalamus and pituitary by cytokines and a reduction in the negative feedback loop. The diurnal variation of cortisol secretion is lost, and resources are shifted away from mineralocorticoid and androgen production toward corticosteroid production. ACTH release can also be increased by the influence of endorphinergic pathways and from the acute (but not chronic) administration of morphine. Even with the negative feedback loop in place, during periods of high stress (after major surgery, septic shock), the adrenal cortex is also influenced directly by paracrine pathways, endothelin, atrial natriuretic peptide, or cytokines.

The adrenocortical response to stress has several mechanisms. Cortisol is 90% bound to cortisol-binding globulin, with less than 10% in the free bioavailable form. This cortisol-binding globulin is downregulated by as much as 50% during acute illness, particularly sepsis, making more cortisol available in the free form. Cortisol has been shown to upregulate intracellular glucocorticoid receptors through a positive feedback mechanism. Glucocorticoid receptors have also shown to increase their level of binding activity in skeletal muscle.

All of these mechanisms allow for glucocorticoid production to enable physiologic compensation in periods of acute stress. Glucocorticoids increase blood glucose levels via hepatic gluconeogenesis, and inhibit adipose tissue glucose uptake. They stimulate free fatty acid and amino acid release as well as increase proteolysis to supply energy and substrate for stress response.

Glucocorticoids contribute toward the synthesis of catecholamines, allowing for maintenance of cardiac contractility, vascular tone, and blood pressure. They also decrease nitric

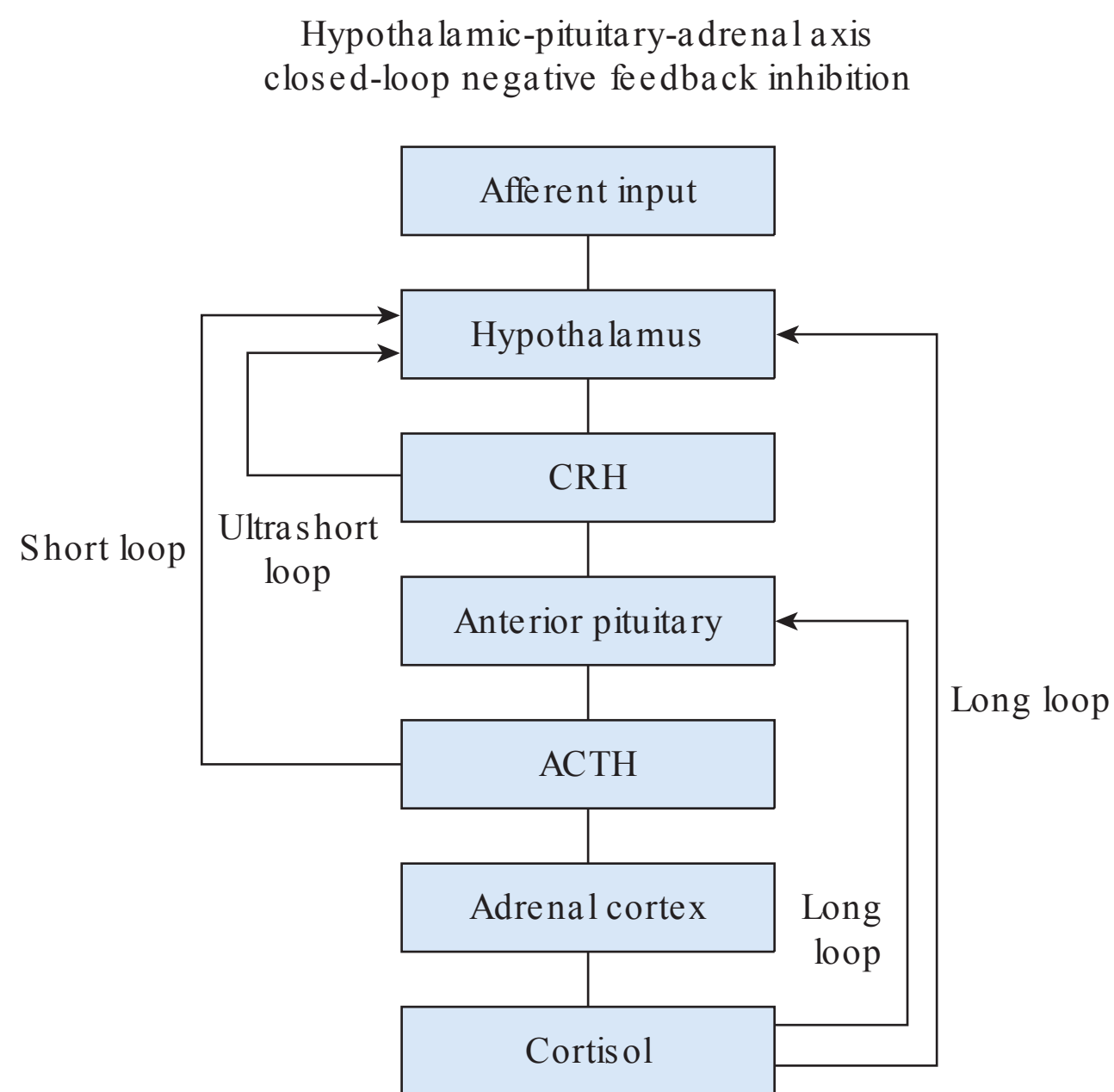


FIGURE 42-1 There are three types of “closed-loop” negative feedback systems in the hypothalamic-pituitary-adrenal (HPA) axis. Corticotropin-releasing hormone (CRH) acts directly on the hypothalamus to control its own secretion in the ultrashort-loop system. Adrenocorticotrophic hormone (ACTH) feeds back on the hypothalamus in the short-loop system. Glucocorticoids exert a negative feedback on the anterior pituitary and hypothalamus in the long-loop system.

oxide and prostaglandin production, with the result of maintaining hemodynamic stability. Glucocorticoids also have anti-inflammatory and immunosuppressive qualities through their downregulating influence on lymphocytes, natural killer cells, monocytes, macrophages, eosinophils, neutrophils, mast cells, and basophils.

In spite of the beneficial actions of cytokines and cellular mediators in an acute stress response, there is evidence that these cytokines and mediators can also have the opposite effect, resulting in decreased ACTH production, impaired corticosteroid production, and an increase in cortisol half-life, which may represent decreases in the number, expression, and function of glucocorticoid receptors. In short, mediators released in the septic patient can have a positive or negative effect on adrenal response, and the net effect may depend on timing, severity of illness, and/or extent of mediator production.

In primary adrenal insufficiency, the adrenal gland fails to produce cortisol. In addition to autoimmune and infectious etiologies, this can be caused by bilateral adrenal hemorrhage, metastases, sarcoidosis, amyloidosis, adrenalectomy (such as in the case of resistant Cushing syndrome), acquired immune deficiency syndrome (AIDS), antiphospholipid syndrome, or medication-induced effects (such as antineoplastics, etomidate, ketoconazole, and mifepristone).³ Secondary adrenal insufficiency, in which the pituitary gland produces insufficient ACTH, is typically caused by a regional tumor, autoimmune causes, genetic mutations, pituitary apoplexy

postpartum (Sheehan syndrome), head trauma, or chronic exogenous glucocorticoid administration.

A life-threatening episode of acute adrenal insufficiency typically manifests in severe hypotension, acute abdominal pain, vomiting, and fever. Hypoglycemic seizures may present in pediatrics or recurrent hypoglycemia in patients with type 1 diabetes. The common clinical signs of chronic adrenal insufficiency include fatigue, energy loss, reduced muscle strength, increased irritability, weight loss, nausea, and anorexia. Primary adrenal failure will likely result in hyperpigmentation, due to the stimulation of melanocytes by ACTH, whereas secondary adrenal failure will manifest with pale skin color. Mineralocorticoid deficiency may also be present, resulting in hyponatremia, hyperkalemia, dehydration, hypovolemia, hypotension, and prerenal failure.

CRITICAL ILLNESS–RELATED CORTICOSTEROID INSUFFICIENCY

The holy grail of adrenal insufficiency in critically ill patients is the question of how to assess adrenal function. Notwithstanding the myriad of effects that can be affected by cytokines and mediators on the HPA axis, we are so far unable to test end-organ effects of cortisol; thus, the diagnosis is commonly based on serum cortisol levels. This has resulted in a variety of studies and beliefs about the most accurate method to assess the serum cortisol level and its subsequent clinical implications.⁴ The cosyntropin test has been used in the past to evaluate for inadequate serum level of cortisol before and 30 and 60 minutes after injection, but the current recommendation from the Surviving Sepsis Campaign (SSC) suggests not to use the cosyntropin test, as it has not proved accurate to identify patients in septic shock who would benefit from steroid administration.⁵

It is important to recognize that the increase in cortisol following a stimulation test is indicative of reserve levels of cortisol, as opposed to adrenal function. The best way to determine whether or not the HPA axis is functioning adequately is to test the entire axis, which, in the case of severely stressed critically ill patients, is already taking place via the stressors of hypotension, hypoxemia, fever, and hypoglycemia. Therefore, a random cortisol level in the face of critical illness should provide adequate information on adrenal insufficiency. A random cortisol level greater than 25 mcg/dL is considered to indicate adequate HPA axis functioning, based on the fact that patients with trauma, surgery, and critical illness have been found to have cortisol levels in the 30 to 50 mcg/dL range that can last for a week. It is also worth noting that critically ill patients lose the diurnal nature of cortisol secretion; thus, timing of a random level should not be an issue.

Adrenal insufficiency can manifest in critically ill patients up to an incidence of 77%, depending on the criteria. Previous steroid use, irrespective of the dose and duration of use, may contribute to suppression of the HPA axis.⁶ Immunosuppression and other infections, while not necessarily causing primary adrenal insufficiency in the outpatient setting, have become the most significant etiology of such in the

critically ill patient. It is also noteworthy that patients with sepsis and systemic inflammatory response syndrome (SIRS) criteria commonly manifest primary adrenal failure, consisting of suppression of the HPA axis as well as glucocorticoid receptor expression. This has been shown to be reversible on resolution of the septic episode.

There is general agreement that adrenal insufficiency in the critically ill patient portends a higher mortality, and that some level of steroid treatment improves outcome. The difficult questions to clarify become how to assess for adrenal insufficiency, at what cutoff level does the patient require steroids, and what dosing should be used. The current recommendations for adult septic shock patients recommend not to administer steroid therapy for adults in septic shock, unless fluid administration and vasoactive agents have not been effective in treating hypotension.⁵ If steroid therapy is indicated, the recommended dosing is hydrocortisone 200 mg/day, in continuous infusion or divided doses.⁵ Each intensive care unit (ICU) should have a standardized protocol for deciding when it is appropriate to start steroids and how to administer them.

It is also worth noting that there are many drug–drug interactions that may occur with steroid administration. Glucocorticoids can decrease the drug blood levels of aspirin, warfarin, insulin, isoniazid, and oral hypoglycemic agents, but they can increase the levels of cyclophosphamide and cyclosporine. Drugs that can increase the level of glucocorticoid blood concentration include antacids, carbamazepine, cholestyramine, colestipol, ephedrine, mitotane, phenobarbital,

phenytoin, and rifampin, while cyclosporine, erythromycin, oral contraceptives, and troleandomycin increase them.

Steroid administration should be tapered as the critically ill patient's clinical picture improves to avoid hemodynamic and immunologic rebound. Hydrocortisone is the corticosteroid of choice, since most studies were performed using this formulation, and it is the closest in physiologic characteristics to cortisone. Hydrocortisone also has mineralocorticoid activity, which must be considered and replaced if other glucocorticoids are utilized.

In summary, critical illness–related corticosteroid insufficiency (CIRCI) can be a significant factor in the progress of the critically ill patient, but many questions remain unanswered at this time. It is important to have a protocolized practice in the care of these patients and to participate in, and follow, the research advances in this very important topic.

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INFECTIOUS DISORDERS

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Approach to Fever in Critical Care

Marnie E. Rosenthal

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PART 1: FEVER IN THE ICU: BACKGROUND AND PATHOGENESIS

Introduction

Fever is an adaptation mechanism of the body in response to internal and external environmental stressors, and is a key indicator of immune system activation. Normal body temperature is maintained by peripheral nerves, which transmit signals back to the hypothalamus. Fever occurs when cytokines cause an increase in body temperature in association with a rise in hypothalamic set point, and consists of three clinical phases: chill, fever, and flush. Elevated body temperatures can broadly be classified as hyperthermia syndromes and infectious and noninfectious fever (Table 43-1). Hyperthermia occurs when thermoregulatory mechanisms fail; when heat production exceeds heat loss through either overproduction of heat or decrease in heat loss. Such examples of heat overproduction include thyrotoxicosis, pheochromocytoma, adrenal crisis, or salicylate toxicity via interruption of the citric-acid cycle and uncoupled oxidative phosphorylation. Heatstroke or anticholinergic toxicity is mediated by a deficiency in mechanisms of heat dissipation. Some hyperthermia syndromes fall into both categories, such as postanesthesia neuroleptic malignant syndrome, and may cause profound hyperpyrexia. It is important to differentiate fever from hyperthermia because hyperthermia due to thermoregulatory failure is treated by a lowering of the body temperature by physical mechanisms (conduction, convection, evaporation); antipyretics are not effective. Both noninfectious and infectious causes of elevated body temperatures in the intensive care unit (ICU) will be discussed in detail in the following sections.

Definition

The average body temperature set point is 37.0°C (98.6°F) and may vary by 0.5°C to 1.0°C according to time of day or hormonal milieu: it is highest at 6:00 a.m. and for women at the time of ovulation. Fever is defined in multiple ways. It is an isolated core body temperature > 38.0°C (100.4°F) or two consecutive elevations of greater than 38.3°C (101.0°F). In neutropenic patients, fever may be defined as a single temperature greater than 38.3°F (101.0°F) or greater than 38.0°C (100.4°F) for 60 minutes. The American College of Critical Care Medicine and the Infectious Diseases Society of America (ACCM/IDSA) define a fever as a rise in body temperature greater than 38.3°C (101.0°F) and recommend any new fever be investigated.¹ However, in immunocompromised or elderly individuals, a lower cutoff may be appropriate, as these patients may not be able to mount substantial febrile responses. Additionally, the fever response may be attenuated in patients with azotemia, congestive heart failure (CHF) or patients receiving antipyretics or pain control with an antipyretic combination.

Epidemiology

Fever is common in critically ill patients and warrants clinical attention. Infections are the leading cause of temperature elevation in hospitalized patients, whereas hypothalamic disorders are less common. In patients admitted to an ICU with severe sepsis, the incidence of fever approached 90%.² Prospective and retrospective studies have described wide ranges of fever prevalence in the ICU, ranging from 30% to 70%, with the highest incidence seen in noncardiac surgical



TABLE 43-1: Causes of Fever in the ICU

Excessive heat production	Delirium tremens, exercise, heatstroke, malignant hyperthermia, neuroleptic malignant syndrome, pheochromocytoma, recreational drugs (cocaine, phencyclidine, methylenedioxymethamphetamine [Ecstasy] lysergic acid diethylamide [LSD]) salicylates, serotonin syndrome, seizure, tetanus, toxicity
Disordered heat dissemination	Anticholinergics, dehydration, heatstroke, neuroleptic malignant syndrome
Hypothalamic	Encephalitis, granulomatous disease (sarcoid and tuberculosis [TB]), neuroleptic malignant syndrome, thrombotic disease, trauma, tumors
Infections	Bacteremia, catheter-related infections, central nervous system infections, <i>Clostridium difficile</i> -associated diarrhea, fungal infections, parasitic infections, pneumonia, postoperative fever, septic thrombophlebitis, sinusitis, surgical site infections, urinary tract infection, viremia

patients in one study.^{3,4} In the neuro-ICU the incidence of fever may approach 70%, only half of the fevers being due to infection, mainly nosocomial pulmonary infection.⁵ The incidence of hyperpyrexia due to anesthesia-induced malignant hyperthermia estimates range from 1:250 to 1:250,000, with a recent study evaluating 2001 to 2005 New York State discharge data establishing local incidence as 1 in 100,000.⁶

Pathogenesis

The earliest published observations regarding temperature regulation appeared in 1912, describing thermal sensitivity of the hypothalamic region.⁷ Further understanding was provided in the 1960s with three influential papers describing the role of the preoptic area of the anterior hypothalamus in thermoregulation.⁸⁻¹⁰

Basal metabolic activity in the liver and heart accounts for the majority of the body's heat production, while the skin accounts for the majority of heat dissipation. The lungs add a minor amount to basal metabolic heat dissipation through conduction and evaporation. Temperature is regulated not by one single neural area, but by feedback loops involving the hypothalamus, brainstem, and spinal cord, which interact with the autonomic, somatic, and endocrine system (Figure 43-1). Stimulation by the anterior hypothalamus causes vasoconstriction and sweating, while posterior hypothalamic activation induces shivering. Vasoconstriction in response to an increased hypothalamic set point begins in the hands and feet as blood is shunted centrally. Shivering develops as a heat conservation mechanism to increase heat production from skeletal muscle. The nature of the response depends on ambient temperature; animal models injected with exogenous substances which raise temperature set point will increase heat production in a cold environment or decrease heat loss in a warm environment.

Fever is regulated at the level of the hypothalamus through pyrogen release by activated immune cells. Exogenous pyrogens, such as lipopolysaccharide (LPS) endotoxin in

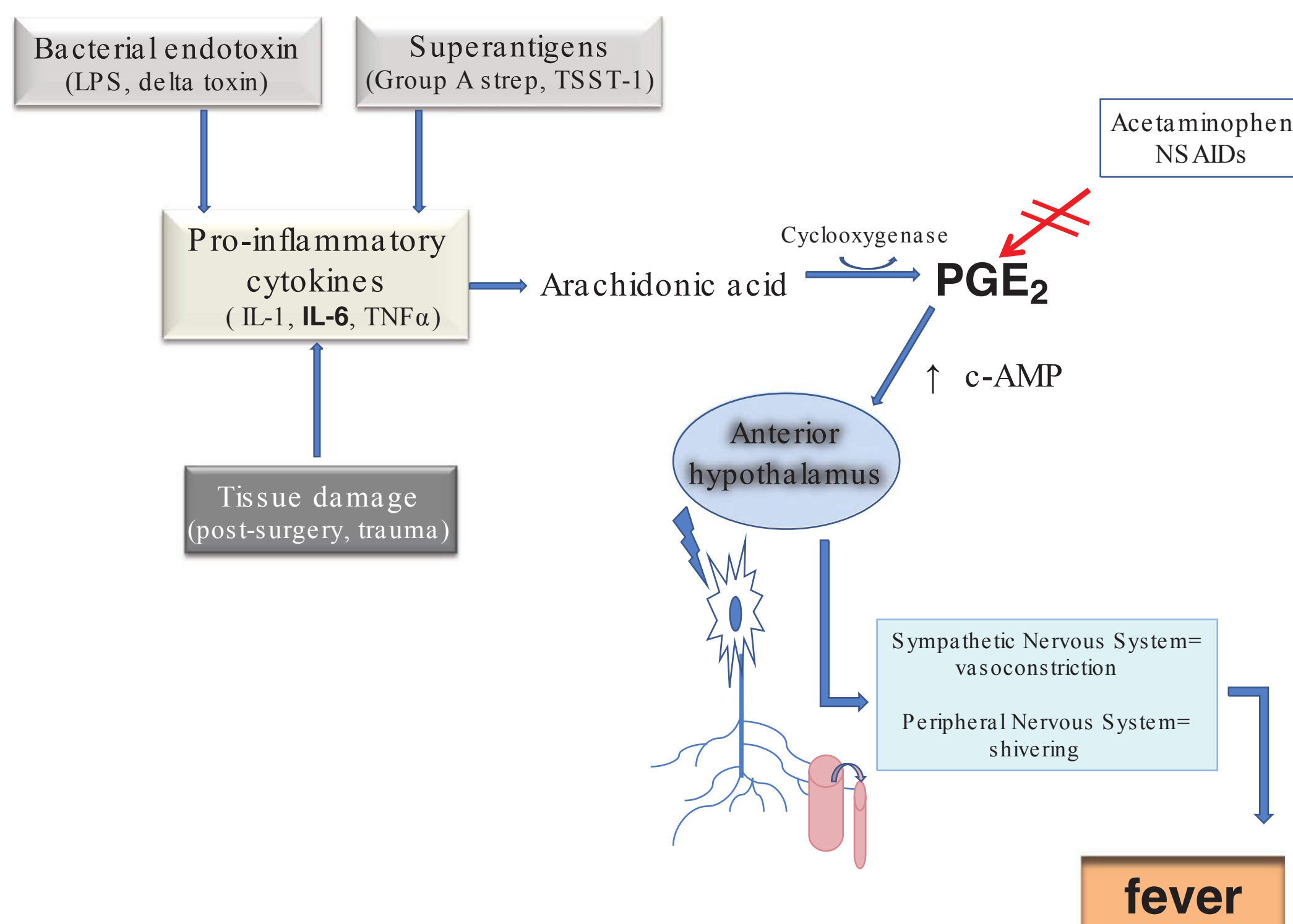


FIGURE 43-1 Pathogenesis of fever.

Gram-negative bacteria or exotoxins such as toxic shock syndrome toxin (TSST) in *Staphylococcus aureus*, trigger febrile responses in the host. LPS complexes with a binding protein and attaches to the CD14 receptor of a macrophage, resulting in cytokine release.¹¹ Cytokines are soluble intracellular signal proteins that regulate local and systemic immune processes. Formulated as large-molecular-weight polypeptides, they are produced by monocytes, macrophages, and glial cells in response to inflammation, infection, or injury.^{12,13} Interleukin (IL)-1 and tumor necrosis factor (TNF) are structurally unrelated cytokines with a strikingly similar biologic function; both are secreted by antigen-presenting cells that augment binding and activation of T cells and promote growth and differentiation of B cells. TNF- α is produced by activated macrophages in response to lipopolysaccharide of Gram-negative organisms, whereas TNF- β is a product of T lymphocytes. Together, IL-1, IL-6, and TNF are collectively referred to as proinflammatory cytokines (Table 43-2).

Endogenous pyrogen, later reclassified as lymphocyte-activating factor and eventually found to be part of the IL-1 family, was the earliest isolated cellular product implicated in fever induction.¹⁴ Animal models of endogenous pyrogens indicate that the febrile response is mediated by activation of calcium channels and can be attenuated by calcium channel blockers such as nifedipine or verapamil.¹⁵ The IL-1 gene family—composed of IL-1 α , IL-1 β , and IL-1 receptor antagonist (IL-1ra)—is encoded on the long arm of chromosome 2. Variable number tandem repeat polymorphisms in this receptor antagonist region are linked to autoimmune dysregulation syndromes such as psoriasis and inflammatory bowel disease.¹⁶ IL-1 β is a potent inducer of IL-6, which is critical in the fever response, as evidenced by the absence of fever production in IL-6-deficient knockout mice.^{17,18} Cytokines bind to and activate their own receptor, activating phospholipase A₂, resulting in release of arachadonic acid, which is the substrate of cyclooxygenase and the rate-limiting enzyme in prostaglandin biosynthesis.¹⁹

Increased levels of IL-1, IL-6, interferon- γ , and TNF- α act on the hypothalamus to raise its inherent set point through the catecholamine cells of the medulla oblongata and the circumventricular organs.²⁰ The organum vasculosum of the lamina terminalis (OVLT) is a vascular sensory organ of the brain that is unique in that it is composed of a capillary

bed that lacks a blood–brain barrier and can therefore monitor the osmotic, ionic, and hormonal environment of the blood.²¹ When pyrogens are detected by the OVLT, prostaglandin E₂ (PGE₂) is released, which triggers the PGE₂ receptor on glial cells to release cyclic adenosine monophosphate (C-AMP). This activates the febrile response via the hypothalamic feedback loops, involving vasoactive substances and neurotransmitters such as norepinephrine, dopamine, and serotonin.²² Additionally, these cytokines are also released during tissue trauma, especially IL-6.²³

Endogenous antipyretics such as IL-10, a protein product of T-helper cells, have been shown in mouse models to inhibit the production of endogenous IL-1 β , IL-6, and TNF during LPS-induced fevers.^{18,24} Additionally, arginine vasopressin, α -melanocyte-stimulating hormone, and glucocorticoids counter and limit the duration of fever.²⁵

Temperature Measurement

In the ICU, body temperature may be measured peripherally or centrally. Temperature is most accurate when measured by thermistors on pulmonary artery catheters (the gold standard), bladder catheters, or esophageal probes. Rectal probes provide a close approximation of core temperature. Generally, readings from rectal thermometers are a few tenths of a degree higher than core temperatures. Rectal thermometers are somewhat invasive for the awake and alert patient and are contraindicated in neutropenic patients. Oral temperature measurements are convenient, safe, and minimally invasive, although readings may be confounded by ingestion of hot or cold fluids, or mouth breathing. Additionally, patients with decreased level of consciousness, arousal states or altered mental status may not be able to comply with placement of a thermometer under the tongue. Readings may vary depending on the location of sublingual thermometer placement, and are generally 0.4°C (0.7°F) lower than rectal temperatures.²⁶ Infrared tympanic membrane thermometers are less accurate than intravascular probes, as well as rectal or oral thermometers. Temporal artery thermometers, and axillary or femoral skin fold temperatures, should not be used to record temperatures in an ICU.²⁷

Effects on the Host

Conflicting evidence exists as to outcome associations with elevated temperature in ICU patients. One study suggested that crude mortality was higher in febrile patients (34.5% vs. 18.7%). However, when adjusted for patient severity, fever was no longer associated with mortality ($p = 0.384$).²⁸ Low-grade fever was common in the ICU, and outcome varied by admission criteria.⁴ High fever was associated with an increased risk of death (20% vs. 12%) in a large literature review.

Numerous studies have found that, after controlling for baseline predictors of poor outcome, fever in acute subarachnoid hemorrhage is independently associated with increased morbidity, including cognitive impairment, and mortality.^{29,30}




TABLE 43-2: Cytokines Involved in Temperature Regulation

Proinflammatory Cytokines	Antipyretic Cytokines
IL-1	IL-4
IL-6	IL-10
IFN- α	Arginine vasopressin
TNF- α	Melanocyte-stimulating Hormone
	Glucocorticoids

IL = interleukin; IFN = interferon; TNF = tumor necrosis factor.

In stroke patients, the earlier the fever onset, the greater the amount of cognitive dysfunction; hyperthermia appearing after 24 hours was not associated with poorer outcome.³¹

Controversy exists as to whether treating a fever is beneficial for the host. Elevated temperatures result in tachycardia, increased minute ventilation, resting energy expenditure, oxygen consumption, and sympathetic tone. Hyperthermia has been associated with rhabdomyolysis, disseminated intravascular coagulation (DIC) and multisystem organ failure.³² In animal models, fever has been shown to decrease the serum level of iron, which is a growth factor for many microbes.³³ It may reduce the expression of virulence factors, enhance antibiotic susceptibility by lowering minimum inhibitory concentrations, and augment host responses.^{34,35} A recent study in a trauma ICU, which randomized patients to permissive or aggressive treatment (650 mg acetaminophen q6h) for fevers $> 38.5^{\circ}\text{C}$, was stopped after the first interim analysis due to a statistically significant increase in deaths in the aggressively treated group ($p = 0.06$).³⁶ Despite the lack of evidence-based outcomes data, pharmacologic and physical means of fever reduction are commonly employed.

PART II: ETIOLOGY OF FEVER IN THE ICU

Noninfectious Causes of Fever

DRUG FEVER

Drug fever is often a diagnosis of exclusion based on the background of administration of a new medication. A hallmark sign of drug fever is the disappearance of fever after the medication is stopped and reappearance after it is restarted. This is most often the result of a hypersensitivity reaction, and commonly occurs 7 to 10 days after the administration of an agent; it may be accompanied by rash, urticaria, or serum sickness. Although any medication can cause hypersensitivity reaction, antimicrobials (especially β -lactams), antimycobacterials, antiepileptics, antiarrhythmics (such as quinidine and procainamide), and antihypertensives (methyldopa and phenytoin) are common causes of fever.³⁷ Certain classes of pharmacologic agents are associated with hyperthermia through disordered thermoregulatory mechanisms. Sympathomimetics, anticholinergics, neurotransmitter-active drugs, such as dopamine antagonists, serotonergic agents, and monoamine oxidase inhibitors, as well as inhaled anesthetics can disrupt the balance between heat production and dissipation. Malignant hyperthermia (MH) occurs in genetically predisposed individuals after exposure to certain pharmacologic agents. It is the result of a large efflux of calcium triggered by inhalation anesthetics or succinylcholine on a background of a genetic defect in the ryanodine, or calcium release channel in the sarcoplasmic reticulum of skeletal muscle.³⁸ Neuroleptic malignant syndrome (NMS) can be seen with antipsychotic agents such as haloperidol, prochlorperazine, metoclopramide, or with the withdrawal of dopaminergic agents. NMS is characterized by muscular rigidity, autonomic dysregulation, extrapyramidal side effects, and hyperthermia,

and is thought to be due to dopamine antagonism within the hypothalamus.³⁹ Serotonin syndrome has similar clinical features, but also involves diarrhea, tremor, and myoclonus. It is related to excessive 5HT_{1A} receptor stimulation, and may be exacerbated with the use of linezolid.⁴⁰ Illicit drugs such as phencyclidine (PCP), Ecstasy (MDMA or methylenedioxymethamphetamine), lysergic acid diamide (LSD), and cocaine have been implicated in hyperthermia syndromes. MDMA ingestion leads to central deregulation of thermogenesis via activation of the sympathetic nervous system and an excessive release of norepinephrine with an uncoupling of adrenoceptors and loss of heat dissipation.⁴¹

HEAD INJURY

Elevated core temperature is common after many types of neurologic injury (ischemic, hemorrhagic, or traumatic) and is associated with increased risk of adverse outcome, even after controlling for confounders or modifiers, such as severity of illness, diagnosis, age, and infection. Human and animal models have shown that fever exacerbates ischemic neuronal damage and is proportional to the degree of pyrexia.⁴² Hyperthermia post-cardiac resuscitation was associated with an unfavorable neurologic recovery after cardiac pulmonary resuscitation.⁴³ Fever was found to be strongly associated with an increased intensive care and overall length of stay (LOS), and higher overall mortality.^{44,45}

HEATSTROKE

Heatstroke occurring in warm environments may be exertional or nonexertional in origin, and may be exacerbated by dehydration or antihistamines. Defined as a core temperature 40°C ($> 104^{\circ}\text{F}$), individuals at the extremes of age are at risk for nonexertional heatstroke during hot weather and heat waves. It is associated with upregulation of heat shock proteins in the brain, which function as molecular chaperones and cellular repair proteins with cytoprotective effects.⁴⁶

NEUROLOGIC CAUSES OF FEVER

Although fever may occur in up to one-quarter of neuro-ICU patients, almost half are noninfectious.⁴⁷ Stroke or subarachnoid hemorrhage can trigger febrile responses in noninfected patients, as can head trauma and neurosurgery involving the floor of the third ventricle.⁴⁸

MISCELLANEOUS

Vasculitis, hyperthyroidism, or mesenteric ischemia can trigger febrile responses in noninfected patients. A low-grade fever can also be seen in the cardiac care unit post-myocardial infarction (MI), resulting from epicardial inflammation after a transmural infarct. Dressler's syndrome, likely mediated by antimyocardial antibodies, can also present with fever and a friction rub up to 2 to 3 months post-MI.

Blood is an irritant; when it accumulates or stagnates, it may induce fever. Hematomas and pulmonary embolism have been associated with fever.⁴⁹ However, contrary to common

dictum, deep vein thrombosis (DVT) is not a common cause of isolated fevers, as evidenced by a number of recent studies evaluating the rate of fever in patients with lower-extremity DVT.^{50,51} Transfusion reactions are possible during or after receipt of blood products.

Noninfectious intra-abdominal processes such as pancreatitis, acalculous cholecystitis and mesenteric ischemia are causes of fever in critically ill patients; these entities frequently present with associated clinical signs and symptoms. Rheumatologic disorders such as systemic lupus erythematosus (SLE) and adult Still disease, as well as occult malignancy are uncommon, albeit possible, causes of fever in ICU patients.⁵²

Infectious Causes of Fever

CENTRAL NERVOUS SYSTEM INFECTION

Focal neurologic abnormalities generally occur with central nervous system (CNS) infection. However, in critically ill patients, a high index of suspicion is warranted even in the absence of focal findings, and appropriate imaging studies and culture data should be obtained.⁵³ Fever is the most common acute presentation of bacterial meningitis in children; in adults and the elderly, confusion, nuchal rigidity, and headache are more common.⁴⁸ Bacterial meningitis may occur after any neurosurgical procedure, but is most common with procedures related to open head trauma.⁵⁴

DIARRHEA

For evaluation of fever in the ICU, ACCM/IDSA defines diarrhea as more than two stools per day that conform to the container in which they are placed.⁵³ Enteral feedings and medications are common causes of loose stool or diarrhea in the ICU patient. The most common enteric cause of fever in the ICU is *Clostridium difficile*, which should be suspected in any patient with fever, elevated white blood cell count, and antimicrobial therapy or chemotherapy administration within 60 days of diarrhea onset. Other organisms that cause fever and diarrhea are generally community associated and rarely acquired after a patient is admitted to an ICU. Therefore, sending stools for routine culture or ova and parasites should be avoided unless the patient was admitted to the hospital with diarrhea, is human immunodeficiency virus (HIV) positive, or as part of an outbreak investigation.⁵³ In patients with negative *C. difficile* toxin assays, it is important to consider increased gastrointestinal (GI) motility as a side effect or medications, enteral feedings, or hemorrhagic enterocolitis due to *Klebsiella oxytoca*.^{55,56}

INTRAVASCULAR DEVICES

Patients should be examined daily for signs of catheter entry-site infections and phlebitis, and any expressed purulence should be sent for Gram stain and culture. Short-term peripheral and noncuffed central catheters should be removed if infection is suspected; with evidence of a tunnel infection or septic physiology, the catheter should be removed, cultured, and reinserted at a different site.⁵³ It is not necessary

to routinely culture all catheters removed from ICU patients, as catheters are frequently colonized within the lumen, which may not correlate with infection.⁵³

PNEUMONIA

Pneumonia is a common cause of infection acquired in the ICU and a predominant cause of fever, especially in mechanically ventilated patients. For initial fever evaluation, a portable chest radiograph is sufficient. In the nonintubated patient, expectorated sputum or nasal/endotracheal aspirate is adequate to evaluate airway colonization or infection.⁵³ Aspirates from the inner channel of the bronchoscope in intubated patients reflect upper airway colonization, and may lead to overtreatment of colonizing organisms. Mini-bronchoalveolar lavage (BAL) or blind bronchoscopy, with a protected brush, is a reliable sampling method to obtain lower respiratory secretions.⁵⁷ Respiratory cultures should be processed within 2 hours of collection.

POSTOPERATIVE FEVER

Fever is a common phenomenon in the first 48 hours after surgery. Initially, the etiology is noninfectious, but after 96 hours, fevers can often be attributed to infectious processes.⁵⁸ Wound infections are rare immediately postop, with the exception of *S. pyogenes* or clostridial infections, which may present in the first three postoperative days. In the febrile postoperative patient, surgical sites should be examined daily for erythema, purulence, or tenderness; incisions should be opened and cultured if infection is expected.⁵³ New or persistent fevers after 96 hours warrant careful surgical-site inspection as well as investigation into other etiologies of fever, including thromboembolic disease, drug reaction, malignant hyperthermia, or catheter-related infection.

SINUSITIS

Nosocomial maxillary sinusitis is a common entity in intubated patients and should be included in the differential diagnosis of fever in an ICU patient.⁵⁹ Either two major criteria (cough, purulent nasal discharge) or one major plus two minor criteria (headache, earache, facial or tooth pain, malodorous breath, sore throat, or wheezing) suggest acute bacterial sinusitis in the outpatient setting. However, in critically ill patients, these signs may not be evident.⁶⁰ Additionally, sinus films may be of limited value and sinus computed tomography (CT) or magnetic resonance imaging (MRI) scans may be difficult to obtain. For a definitive diagnosis, puncture and sampling of the involved sinus under aseptic technique should be performed.⁵³ A prospective study of new onset fever in surgical ICU patients—after excluding bacteremia, catheter-related infections, or pneumonia—found that sinusitis diagnosed by three-view sinus films accounted for 24% of fevers. The predominant microbiology was *Klebsiella* and *Pseudomonas*.⁶¹ Another study found that the common pathogens by maxillary sinus aspirates were *Acinetobacter* (32%) and anaerobes (21%) and that a combination of a nasal decongestant and topical nasal steroid was effective in

decreasing the incidence of sinusitis in mechanically ventilated trauma patients.⁶²

URINARY TRACT INFECTION

Urinary tract infection (UTI) is among the most frequent nosocomial infection in the ICU, and a common cause of fevers due to frequent bladder instrumentation. Not surprisingly, increased duration of catheter days is correlated with the risk of cystitis and pyelonephritis.⁶³ The predominant pathogens involved in UTIs in ICU patients include multidrug resistant Gram-negative rods. Cultures should be collected from the sampling port of the catheter, not the drainage bag, and processed by the microbiology laboratory within 1 hour. A colony count from a catheterized patient of $> 10^3$ cfu/mL represents true infection: Urinary tract infection (UTI).⁵³

IMMUNOCOMPROMISED PATIENTS

Immunocompromised patients (i.e., HIV/acquired immune deficiency syndrome [AIDS], induced immunosuppression from solid organ or bone marrow transplants, chemotherapy, or immunomodulation therapy) are at risk for opportunistic bacterial, viral, and fungal infections. Special consideration must be given to immunodeficient patients with fevers. A broad range of infectious organisms can be seen, including cytomegalovirus, *Pneumocystis jirovecii*, aspergillus and endemic mycoses, such as histoplasma and coccidioides.

Fever in the chemotherapy-induced neutropenic patient is a constantly evolving field of study with regard to both diagnosis and management. Neutropenic fever with an isolated single oral temperature of 38.3°C (101.0°F), or a sustained temperature greater than 1 hour of 38.0°C (100.4°F) in the immunocompromised host deserves prompt action and empiric broad spectrum antibiotic coverage, to be discussed in further detail later.

PART III: DIAGNOSIS AND MANAGEMENT OF FEVER IN THE ICU

Diagnostic Approach

Approach to the febrile patient begins with a proper diagnosis and management of the underlying disorder. Pseudosepsis, characterized by fever, elevated leukocyte counts with a left shift, and sepsis physiology with elevated heart rate and hypotension can closely mimic infectious fevers, but may be attributed to rheumatologic, endocrine, or neurologic disturbances. Adrenal insufficiency and thyroid storm have been mistaken for sepsis.⁶³ The magnitude of temperature elevation does not provide clues to the etiology, as fevers greater than 102.0°F may be present with both infectious and non-infectious causes.

Accurate history and physical exam, along with careful review of the hospital course, including previous inpatient or outpatient workup, is the first step in diagnosis and management of the febrile patient in the ICU. The 2008 ACCM/IDSA guidelines recommend that a new onset of temperature

$< 36.0^{\circ}\text{C}$ or $> 38.3^{\circ}\text{C}$ warrants a clinical assessment.⁵³ A thorough physical exam should be performed, including conjunctival and fundoscopic ocular exam, detailed oropharyngeal inspection, careful auscultative cardiopulmonary exam, and full skin exam, including catheter insertion sites and dependent or posterior body surfaces when possible. Radiographic imaging should be employed if clinical signs warrant further investigation. Laboratory investigation based on results of a clinical assessment may include a complete blood count with a differential, complete metabolic panel, urine and sputum microscopy and culture, and additional Gram stain and culture specimens from any concerning site. Blood cultures are the only mandatory evaluation and should follow certain guidelines. According to the 2008 ACCM/IDSA guidelines for evaluation of new fever in critically ill adult patients, within the first 24 hours of a fever, and prior to initiation of antibiotics, three to four blood cultures from separate puncture sites should be drawn after decontamination with 2% chlorohexidine gluconate, preferentially, or 1% to 2% tincture of iodine.⁵³ Patients with intravascular access should have one set drawn through the line and one set drawn peripherally. Access to the intravascular device and stopper on the blood culture bottle should be swabbed with 70% alcohol and allowed to dry for 30 seconds prior to drawing 20 to 30 mL of blood for inoculation. Additional blood cultures should be drawn only for a suspicion of continuation or recurrent bacteremia or for a test of cure 48 to 96 hours after appropriate antimicrobial or antifungal therapy.

Special Considerations: Neutropenic Patients

Risk stratification is an important first step in managing patients with fever and neutropenia, whether in the outpatient, inpatient or ICU setting. Since the initial publication of the IDSA Clinical Practice Guideline for the Use of Antimicrobial Agents in Neutropenic Patients with Cancer in 1997, updated in 2002 and again in 2011, recommendations regarding diagnostic techniques and management strategies have been evolving.^{65–67} A high suspicion for antibiotic-resistant organisms in critically ill patients, with empiric coverage for vancomycin-resistant enterococcus (VRE), methicillin-resistant *Staphylococcus aureus* (MRSA), extended-spectrum β -lactamase (ESBL) and carbapenemase-resistant Enterobacteriaceae (CRE) organisms, including *Klebsiella pneumoniae* carbapenemase (KPC) should be based on hospital endemicity and resistance patterns as well as patient's prior colonization or infection history. De-escalation to targeted therapy should be instituted as early as clinical and microbiologic data allow. In neutropenic patients with continued unexplained causes of fever, continuation of empiric antimicrobial therapy should continue until the ANC recovers to > 500 cells/mm³.⁶⁷

Antipyresis

Despite a lack of compelling evidence-based medicine, fever is commonly treated by pharmacologic and physical

mechanisms to establish euthermia in the ICU. Rationale for treating hyperthermia include therapeutic effect on metabolic consumption and patient comfort. In one study, external cooling was shown to decrease oxygen consumption by 20% in febrile critically ill patients if treated with paralytics to prevent shivering; however, if shivering was not inhibited, external cooling was shown to increase oxygen consumption.⁶⁸ In a large clinical trial, treatment with intravenous ibuprofen reduced core temperature, heart rate, oxygen consumption, and lactic acid blood levels, but did not decrease organ failure or 30-day mortality.⁶⁹

The goal of treating fever is to reduce the hypothalamic set point and to restore the balance of heat production and dissipation. Pharmacologic therapy includes nonsteroidal anti-inflammatory drugs (NSAIDs) and steroids, while physical mechanisms range from externally applied cooling blankets, fans, or ice packs, to chilled intravenous fluids, gastric lavage, or intravascular catheter-based techniques. NSAIDs and acetaminophen/paracetamol inhibit the cyclooxygenase pathway and formation of prostaglandin E₂, and foster a return to a normothermic hypothalamic set point.⁷⁰ Aspirin and NSAIDs effectively reduce fever, but can have an anticoagulant effect on platelets. Acetaminophen is the preferred antipyretic in adults, but increases the risk of Reye syndrome in children, thus should be avoided in children. If bacteremia or infection is suspected, targeted antimicrobial therapy should be initiated and de-escalated as appropriate microbiologic information becomes available.

Drug hypersensitivity reactions should be treated with medication withdrawal. Malignant hyperthermia should be treated with immediate withdrawal of the anesthetic agent in conjunction with intravenous dantrolene and procainamide to prevent ventricular arrhythmia.

Special Considerations: Antibiotic Choice in Neutropenic Patient with Fever

According to the 2011 updated practice guideline regarding antimicrobial agents in neutropenic patients with cancer published by IDSA, first-line single-agent antimicrobial treatment with an antipseudomonal β -lactam antibiotic—such as cefepime, piperacillin-tazobactam or a carbapenem—is recommended. Additional antimicrobials (aminoglycosides, fluoroquinolones, and/or vancomycin) may be added to the initial regimen for level of severity or complications such as hypotension and pneumonia, or if a high likelihood of a multidrug-resistant organism is suspected or identified.⁶⁷ Additionally, vancomycin is not recommended universally as part of the initial antibiotic choice for fever and neutropenia, with the exception of suspected catheter-related infection (including tunnel site erythema, port-a-catheter pocket fluctuance or breakdown), skin or soft-tissue infection, pneumonia, or hemodynamic instability.⁶⁷ Empiric antifungal coverage should be considered after 5 to 7 days of persistent or recurrent fevers.

CONCLUSION

Fever is a well-preserved adaptive mechanism that may provide a survival benefit to the host. It is a common, non-specific physical exam finding in the ICU, which warrants attention. An automatic and protocol drive toward normothermia should be avoided, as the etiology differs depending on underlying medical or surgical factors. Appropriate interventions range from careful observation to immediate and aggressive action, and should be decided on a case-by-case basis; no single “fever workup” should be implemented across all patient populations.

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Principles of Antimicrobial Use in Critical Care

Patrick J. Cahill • Manjari Joshi

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Critically ill patients are at very high risk of developing severe infections, with incidence rates five to ten times higher than general wards.¹ Data from US hospitals covering 2009 to 2010 showed that, although patients in critical care wards represent only 15.1% of the hospital population, they developed almost 43% of healthcare-associated infections (HAIs). Approximately 65% of all device-related HAIs occurred in intensive care unit (ICU) settings.^{1,2}

Critically ill patients have numerous insults to normal host mechanisms. Peripheral and/or central access devices or wounds usually compromise skin integrity. Certain immunosuppressive medications decrease the ability of the immunologic defenses to function properly. Furthermore, other underlying medical conditions, such as diabetes, malnutrition, and renal disease, may predispose patients to infectious complications.

Antimicrobials are consistently among one of the most important and commonly prescribed drugs; appropriate policies for their use must exist in the ICU. A survey of antibiotic usage in the United States from 2011 demonstrated that almost 50% of all patients in hospitals received at least one antibiotic medication. This number approached 75% of patients in critical care settings.^{2,3} The success of these drugs is dependent on many factors; therefore, it is imperative for healthcare providers to have a clear understanding of antimicrobial use in the critically ill patient.

General principles of antimicrobial use in critical care should include the following³⁻⁵:

- *Healthcare providers need to have a clear understanding that all fevers and leukocytosis are not always caused by infections.* Systemic inflammatory response syndrome (SIRS) can be due to many noninfectious causes; thus, empirical antimicrobials are not always indicated.

- Pursue diagnostic studies for both infectious and noninfectious causes until a diagnosis is reached.
- Always attempt to arrive at a diagnosis for the syndrome encountered.
 - Clinical outcomes are improved when a diagnosis is reached and targeted therapy is provided.
- Develop an empirical antimicrobial therapy based on differential diagnosis and predicted mortality.
 - Treat patients with sepsis with broad-spectrum antibiotics empirically.
 - Modify therapy to the most narrow-spectrum antibiotic when site and microbiology of the infection is defined.
 - Source control is essential for optimal care.
- Appropriately dose antimicrobials to achieve adequate dosing and minimize toxicity.
 - In cases of sepsis, early and appropriate administration is essential to improve survival.
 - Modify doses in patients with renal or hepatic dysfunction.
 - Have awareness of drug interactions with other medications.
- Define and continually address duration of antimicrobial therapy.
 - Tailor therapy based on microbiologic results and clinical response.
 - Discontinue antimicrobials if a noninfectious etiology is documented.
 - Base duration of therapy on clearly established standards.
- Address antimicrobial resistance, including use of surveillance cultures.
 - Antimicrobial stewardship is needed.

EVALUATION OF FEVER IN CRITICAL CARE

There are several considerations when evaluating a critically ill, febrile patient.⁶ The normal human body temperature is 37 ± 0.5 to 1°C , and may be affected by environmental or therapeutic factors. These could include specialized mattresses, air conditioning, and lighting. Interventions such as cardiopulmonary bypass, hemodialysis, and continuous hemofiltration will alter a patient's normal fever curve. In addition, there are many patient factors that may contribute to an inability to mount an effective febrile response, such as congestive heart failure, chronic liver or renal disease, and anti-inflammatory or antipyretic medications.

The pulmonary arterial catheter thermistor is generally considered the gold standard for measuring a patient's temperature. Regardless of the device used, it should be reliable and regularly calibrated. It is important to use a standard definition of fever as well: some institutions define a fever as a temperature $\geq 38.3^\circ\text{C}$ on two consecutive readings. In neutropenic patients, a single oral temperature $\geq 38.3^\circ\text{C}$, or $> 38.0^\circ\text{C}$ for 1 hour is sufficient to call it a fever.

A thoughtful clinical evaluation of the febrile patient is the most important tool used in a workup. After a careful chart review and physical examination, proceed to laboratory and radiographic investigations. Almost every workup is going to include blood cultures unless initial examination suggests a noninfectious cause. In the trauma patient, one must always be mindful of the possibility of missed injuries and retained foreign bodies, such as tampons. Site-specific investigations include the following:

- Intravascular devices are one of the most common causes of HAIs, accounting for more than 40% of HAIs. A careful assessment of all venous and arterial catheters is important.
- Pneumonia, including ventilator-associated pneumonia (VAP), is another important cause of morbidity and mortality.
- Urinary tract infections (UTIs), specifically those associated with indwelling catheters, need to be considered as potential sources. Urinary catheters should be reevaluated daily for continued need.
- The gastrointestinal (GI) tract is an important consideration, especially in the setting of diarrhea and recent antibiotic use. *Clostridium difficile* is increasingly becoming a burden, and is another reason for prudent antibiotic usage.
- Sinusitis is something that ICU patients are at risk for because of the frequent use of nasogastric tubes.
- Intracranial infections are an unusual source of fever in the hospitalized patient without trauma or instrumentation in the head.
- Surgical-site infections may account for up to 25% of the cost of nosocomial infections, and are even more frequently a source of fever.

Fever in the critical care patient is frequently noninfectious in origin. Common causes include:

- Medications (drug fever)

- Alcohol or drug intoxication or withdrawal
- Aspiration pneumonitis
- Venous thromboemboli or pulmonary emboli
- Arterial occlusion, including acute myocardial infarction (MI) and ischemic bowel
- Bleeding, including central nervous system (CNS) hemorrhage
- Acute respiratory distress syndrome (ARDS)
- Acalculous cholecystitis

CHOICE OF THE PROPER ANTIMICROBIAL AGENT

A number of factors must be considered in choosing the appropriate antimicrobial for a given infection. These can be grouped into three major categories: microbial, host, and drug factors.

Microbial Factors

It is important for healthcare professionals to have some knowledge about the identity of the infecting organism or at least make a reasonable guess at its identity from available information. It is useful to know what organisms cause infections in that particular ICU. For example, it is a known fact that *Staphylococcus aureus* and *Pseudomonas aeruginosa* are the most common infecting agents in special units, such as burn units. Second, information about the susceptibility of the infecting/likely organism should be as current as possible. An antibiogram, updated regularly by the local microbiology lab, can be an important tool for appropriate antimicrobial selection. It is also imperative for healthcare professionals to be well informed about important characteristics of certain microbes, such as toxin-producing strains of staphylococci, streptococci, or clostridia. In many instances, antibiotics are started without the exact knowledge of the infecting organisms. In such cases, familiarity with the specific characteristics of the organisms could help with selection of appropriate antimicrobial therapy. For instance, a healthy person with a rapid onset of cellulitis most likely has an infection caused by toxin-producing strains of streptococci or staphylococci. Management should include aggressive surgical debridement and antimicrobial therapy, such as clindamycin, targeted toward the toxin production.

Host Factors

A number of host factors influence antimicrobial efficacy, toxicity, and the selection of antibiotic therapy:

- History of allergies to previous antimicrobial agents
- Age: Many physiologic functions, such as renal capacity, decline with age. Absorption of certain antibiotics, for example, penicillin G, varies with age. Several adverse effects have also been noted to occur with increased incidence in older adults. In some cases, this may be due to specific disease states or impairment of physiologic processes. However, in certain cases, the

only identified factor is age. An example is the increased hepatotoxicity of isoniazid observed with age.⁷

- Renal or hepatic abnormalities: The kidneys and liver serve as the major routes of excretion of antimicrobials. In patients with impaired renal and/or hepatic function, toxic levels of antibiotics can cause severe side effects.
- Pregnancy: All antibiotics cross the placenta to a varying degree, and many antibiotics are also secreted in breast milk. Therefore, the fetus or infant can be exposed to adverse effects of a drug.^{8,9}
- Genetic or metabolic abnormalities: In certain individuals, the presence of genetic or metabolic abnormalities may also have a significant effect on the toxicity of a given antimicrobial agent.¹⁰ Examples include acetylation of certain drugs in Asians and potentiation of hypoglycemic effects of sulfonylureas by sulfonamides in diabetics.
- Site of infection: For antimicrobial therapy to be effective, an adequate concentration of the drug must be delivered to the site of infection usually at least equal to the minimum inhibitory concentration (MIC) of the organism. Other considerations include the following^{11–13}:
 - Protein binding of the drug
 - Antibiotic penetration to various sites, for example, blood–brain barrier in meningitis
 - Local factors, such as the presence of pus and devitalized tissue, can lead to inactivation of certain antibiotics. Foreign bodies can serve as a nidus for microbes to adhere and produce biofilms, as seen in prosthetic joint infections. In addition, changes in oxygen tension and pH, especially in the urinary tract, can serve to enhance the effect of certain antibiotics, such as aminoglycosides or nitrofurantoin, at either alkaline or acidic environments, respectively.

Drug Factors

Antibacterial drugs are usually divided into two groups: those that are primarily bacteriostatic (inhibit growth of the organism) and those that are primarily bactericidal (kill the organism). Bacteriostatic drugs require the aid of host defenses to clear tissues of the infecting organism. In cases in which the host defenses are deficient or impaired at the site of infection, for example, meningitis and endocarditis, the organism will resume growth on stopping the bacteriostatic drug. These circumstances require the use of bactericidal drugs; in most other infections, bacteriostatic drugs are sufficient. In more recent decades, it has become apparent that pharmacokinetic (PK) and pharmacodynamic (PD) properties are the major determinants of in vivo efficacy of antimicrobial agents.¹⁴

PHARMACODYNAMIC PROPERTIES

Antimicrobial PD properties seek to measure drug exposure with microbiologic or clinical effects.¹⁵ For certain antibiotics, the rate of killing is closely related to the length of time that the concentration of the drug is sustained above breakpoint MIC (time-dependent activity); for other antibiotics, killing rates are more related to the peak concentration above breakpoint

(concentration-dependent activity).¹⁶ Many antibiotics also demonstrate suppressive effects on bacterial growth even after their concentrations have fallen below the MIC. This is described as the postantibiotic effect (PAE). Based on this, there are three largely recognized patterns defining the PK/PD properties of the major classes of antibiotics.^{17–19}

1. Time-dependent killing and minimal to moderate PAE. The amount of time that free antimicrobial concentrations remain above the MIC ($T > \text{MIC}$) for the organism is the PK/PD index correlating with efficacy. β -lactams exhibit this pattern of activity.
2. Time-dependent killing and prolonged PAE. This goal of dosing is to optimize the amount of drug, and the area under the concentration–time curve at 24 hours/MIC ($\text{AUC}_{0-24}/\text{MIC}$) ratio. This is the index most closely associated with efficacy. Antimicrobials such as linezolid, vancomycin, and tigecycline represent this class of drugs.
3. Concentration-dependent killing and a prolonged PAE. The peak concentration/MIC ($C_{\text{max}}/\text{MIC}$) ratio and/or $\text{AUC}_{0-24}/\text{MIC}$ ratio are the best PK/PD parameters correlating with efficacy. This is predictive of activity of aminoglycosides, fluoroquinolones, metronidazole, and daptomycin.

PHARMACOKINETIC PROPERTIES AND CRITICAL ILLNESS

PK properties describe the time course of drug levels in the body as a result of absorption, distribution, and elimination. Critically ill patients are subject to several pathogenetic conditions that may substantially alter the PK properties of antimicrobials that, in turn, can influence the efficacy of the drug. Most often, variations in the volume of distribution and renal or hepatic function are the most common pathogenetic conditions affecting drug disposition in critically ill individuals.

Volume of Distribution and Drug Concentrations

In many instances in critical illness, the volume of distribution is usually greater than in noncritically ill patients. This is usually as a result of increased capillary permeability resulting from endothelial damage as well as reductions in oncotic pressure from hypoalbuminemia, all leading to fluid extravasation. This is particularly important when dealing with hydrophilic antibiotics such as β -lactams, aminoglycosides, and vancomycin. These antibiotics are distributed primarily in the extracellular fluid (ECF); in cases of significant interstitial extravasation, the plasma levels may drop substantially, resulting in clinical failure. This has been well described with aminoglycosides that are concentration-dependent bactericidal drugs.^{20,21} It is therefore important to monitor drug concentrations and consider higher doses for most hydrophilic antibiotics when an edematous state is present.^{22,23} On the other hand, with lipophilic antibiotics such as quinolones, which have a large volume of distribution, changes in interstitial fluid volume are not as relevant.



TABLE 44-1: Selected Antimicrobials That Do Not Require Dosage Adjustments in Renal Diseases and Antimicrobials That Require Adjustments in Liver Disease

Antibacterials		Antifungals	Antivirals
Azithromycin	Linezolid	Anidulafungin	Ribavirin
Ceftriaxone ^a	Minocycline	Caspofungin ^a	Many HIV medications ^a
Chloramphenicol ^a	Nafcillin ^a	Itraconazole (solution) ^a	
Clindamycin ^a	Pyrimethamine	Ketoconazole	
Doxycycline	Rifaximin	Micafungin	
Metronidazole	Tigecycline ^a	Voriconazole (oral) ^a	

^aDrugs that require adjustment with hepatic failure.

Renal Dysfunction and Drug Concentrations

Most antibiotics are cleared from the body largely through the kidneys. In critical illness, many patients develop renal impairment that may easily lead to drug accumulation. Furthermore, many patients are supported by renal replacement therapies (RRT), such as hemodialysis or continuous RRT, which clear drugs from the system similar to a kidney functioning with a glomerular filtration rate (GFR) ≤ 35 mL/min. While some antibiotics, such as vancomycin and aminoglycosides, have easily measurable drug levels used as surrogates for toxic levels, many other drugs do not have measurable levels and toxic levels are difficult to ascertain.²⁴

Conversely, the use of hemodynamically active drugs (dopamine) and the hyperdynamic phase of extensive burns or early sepsis can modify renal blood flow with an increase in GFR leading to increased renal clearance of most hydrophilic and lipophilic antimicrobials.²⁵ Finally, in many instances, serum creatinine and estimated clearance often fail to estimate renal function appropriately, and the adjustments may cause an overdose.²⁶ Table 44-1 lists the antimicrobials that do not require dosage adjustment in renal disease.

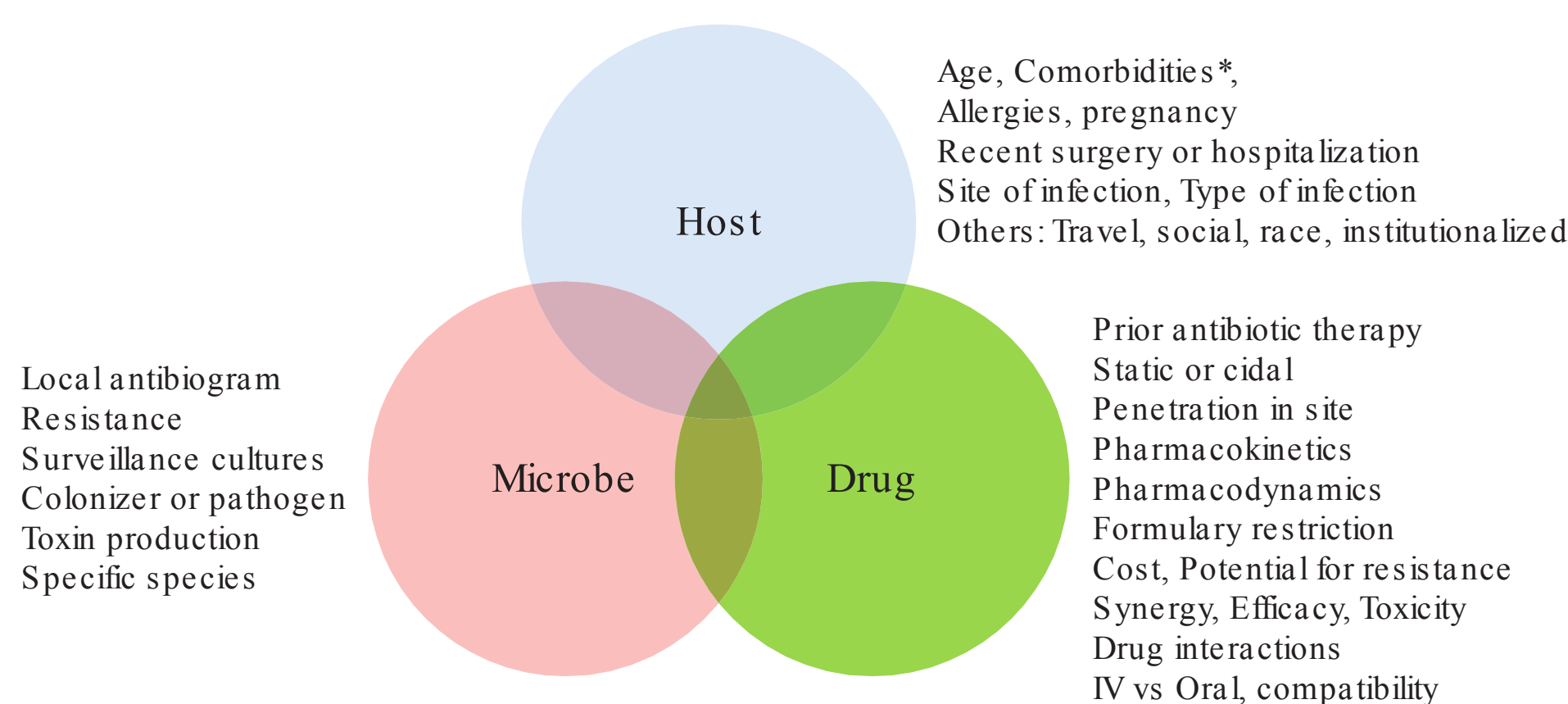
Hepatic Dysfunction and Drug Concentrations

Several antimicrobials have well-documented effects on hepatic function. These are usually categorized into inducers

or inhibitors that can have huge impacts on concomitantly administered drugs. Inhibitors of certain hepatic enzymes—such as erythromycin and ciprofloxacin, which inhibit CYP4A12—can interfere with theophylline metabolism, leading to toxicity. Others—such as rifampin, which induces Cy P450—can result in lowering the levels of other drugs, such as Coumadin (warfarin). The effect of hepatic metabolism on the majority of antimicrobials is very limited and protein binding is also low enough to make no difference in efficacy. Therefore, there is rarely any need to make dose adjustments to many antimicrobials in critical illness with hepatic dysfunction.²⁷

INITIAL SELECTION OF ANTIMICROBIAL THERAPY

Prompt, effective, and targeted antimicrobial therapy is crucial for treating a critically ill patient with suspected infection. Higher mortality is associated with both delay in therapy and inappropriate treatment.^{3,4} Often, critically ill patients present with a nonspecific SIRS that stems from either infectious or noninfectious causes. To define the etiology of the SIRS, a thorough investigation should be undertaken. If the patient is critically ill and an infectious etiology is suspected, antimicrobials should be empirically initiated based on a number of factors. Figure 44-1 provides an overview of the variables



*Comorbidities: diabetes, smoking, obesity, immunosuppression, dialysis, and organ dysfunction

FIGURE 44-1 Variables for decision making for antibiotic choices.

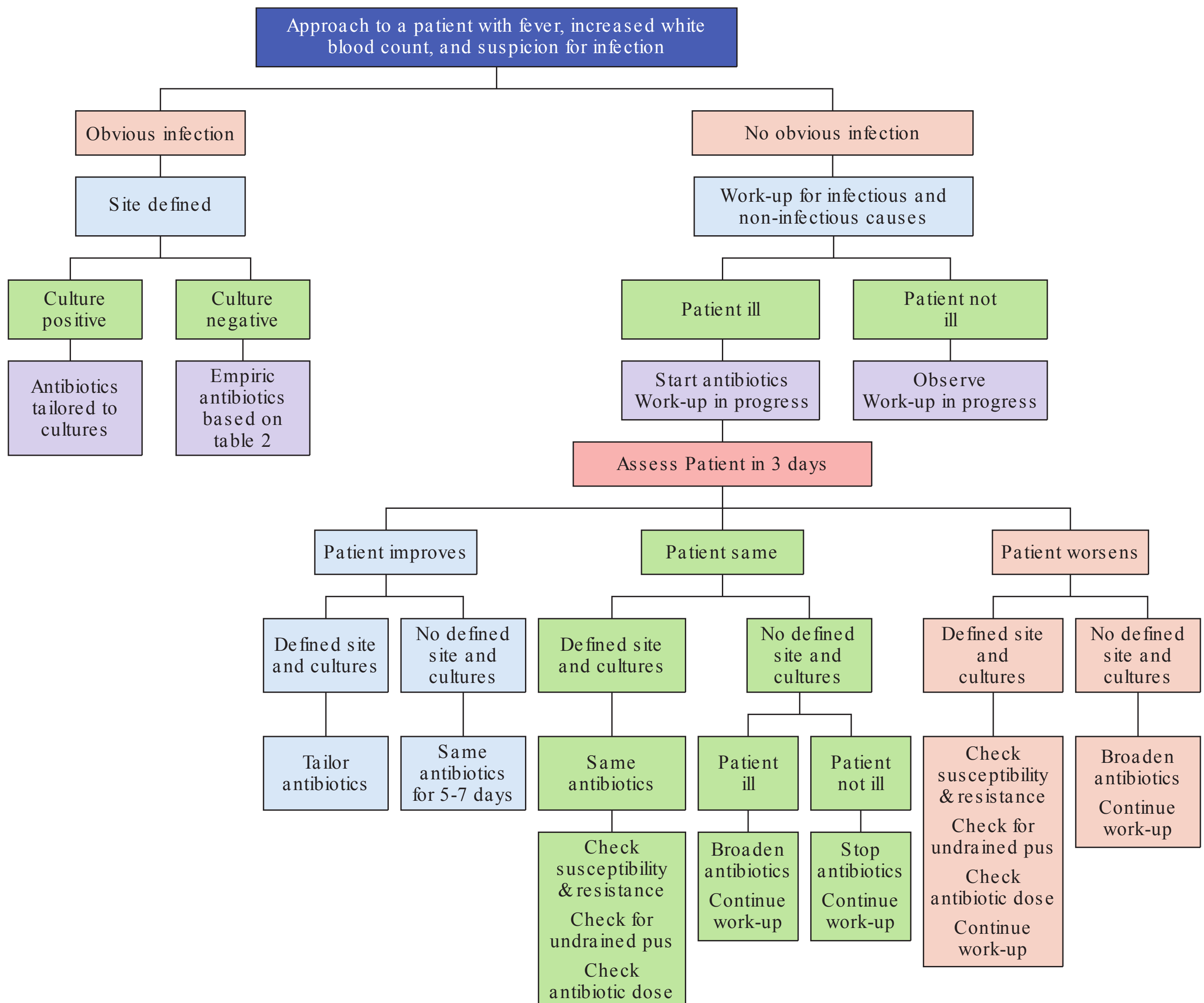


FIGURE 44-2 Approach to a patient with suspected infection.

used in the decision-making process for the selection of antimicrobial agents.

After selection of initial therapy, it is important to evaluate each patient on a daily basis. The evaluation should be comprehensive and include the following assessments:

1. Is the cause of the SIRS infectious or noninfectious?
2. If it is infectious, what is the site of the infection and what organisms (type and susceptibility) are associated with it?
3. Is there adequate source control?
4. Assessment of clinical response to therapy.
5. Modification of therapy based on the clinical data and patient response.
6. Defining the duration of antimicrobial therapy.
7. It is important to stop the antimicrobial therapy if the patient is stable, but is not improving and no infectious etiology of the SIRS is apparent. This is one of the

hardest concepts to accept in a critically ill patient. In this setting, most healthcare providers change antimicrobial therapy or add more potent antibiotics to the existing regimen. This practice masks the underlying SIRS, which contributes to a delay in the correct diagnosis. Additionally, it is associated with antimicrobial-related side effects and the emergence of antimicrobial resistance. During the time period of antimicrobial withdrawal, the patient needs to be closely observed for any signs of clinical decompensation. It is also important to keep evaluating the patient for the etiology of the SIRS.

Figure 44-2 provides an approach to the management of patients with suspected infection.²⁸

Once the site of infection and the causative organisms are identified, antimicrobial therapy needs to be optimized. Table 44-2 provides a summary of the specific organisms and the antimicrobial agents that exert the most activity against

TABLE 44-2: Recommended Antimicrobial Therapy for Selected Pathogens²⁸

Pathogen	Recommended	Alternative	Other Options
Gram-positive cocci			
<i>Staphylococcus aureus</i> (methicillin-sensitive)	Oxacillin Nafcillin	CEPH 1 (cefazolin) Clindamycin Vancomycin	Carbapenems BL/BLI; FQ Linezolid Daptomycin Tigecycline
<i>S. aureus</i> (methicillin-resistant) (health care associated) ^a	Vancomycin	Daptomycin Linezolid Ceftaroline	Tigecycline TMP/SMX (some strains resistant)
<i>S. aureus</i> (methicillin-resistant) (community acquired) ^a • Mild-moderate	TMP/SMX or doxycycline ± rifampin	Clindamycin (if D test is negative)	Vancomycin Daptomycin Ceftaroline Linezolid Tigecycline
<i>S. aureus</i> (methicillin-resistant) (community acquired) ^a • Severe infection	Vancomycin	Daptomycin Linezolid Ceftaroline	
Coagulase-negative staphylococci	Vancomycin ± rifampin	TMP/SMX ± rifampin	Daptomycin ^b Linezolid ^b Tigecycline ^b
<i>S. pneumoniae</i> (penicillin-sensitive)	Penicillin G	Multiple agents	—
<i>S. pneumoniae</i> (penicillin-resistant, MIC ≥ 2)	Vancomycin ± rifampin or levofloxacin/moxifloxacin		For nonmeningeal infections: CEPH 3/4 Linezolid Tigecycline ^b Ceftaroline Daptomycin
<i>S. pyogenes</i> (A, B, C, F, G)	Penicillin G or V + clinda for serious group A strep infections + gent for group B strep infections	All β-lactams All macrolides CEPH 1/2	Macrolide resistance increasing
<i>Listeria monocytogenes</i>	Ampicillin	TMP/SMX	Penicillin G (high dose) Erythromycin APAG (synergy with β-lactams)
<i>Enterococcus</i> (penicillin-sensitive)	Penicillin or ampicillin ± gentamicin	Vancomycin ± gentamicin	—
<i>Enterococcus</i> (penicillin-resistant/ vancomycin-sensitive)	Vancomycin ± gentamicin	Linezolid	Daptomycin Tigecycline
<i>Enterococcus</i> (penicillin-sensitive, vancomycin + streptococci/gent resistant) ^a	Penicillin G Ampicillin Nitrofurantoin or fosfomycin (UTIs only)	Linezolid ^a	Daptomycin Tigecycline
<i>Enterococcus faecium</i> (PCN, AMP, vancomycin + streptomycin/gent resistant) ^a	Linezolid	Quin-Dalfo ± FQ, Combination antibiotics: doxycycline or chloramphenicol	Daptomycin Tigecycline
Gram-negative rods			
<i>Escherichia coli</i> (ESBL producer—same as ESBL <i>Klebsiella pneumoniae</i>)	Recommended agents vary with the clinical setting		
<i>Klebsiella</i> spp. <i>Enterobacter</i> spp. <i>Klebsiella pneumoniae</i> (ESBL producer) ^a	Imipenem Meropenem	CEPH 4	PIP-TZ ^a TC-CL ^a Aminoglycosides ^a

TABLE 44-2: Recommended Antimicrobial Therapy for Selected Pathogens²⁸ (continued)

Pathogen	Recommended	Alternative	Other Options
<i>Klebsiella pneumoniae</i> (carbapenemase producer) ^a	Colistin		Tigecycline ^a Aminoglycosides ^a Combination therapy: Colistin + carbapenem Colistin + tigecycline
<i>Serratia marcescens</i>	FQ Carbapenems CEPH 3/4	Aztreonam Gentamicin	TC-CL PIP-TZ
MDR <i>Acinetobacter</i> (resistant to IMP, FQ, APAG, CEPH 3, AP Pen) ^a	AMP-SB-colistin Amikacin	Polymyxin B Tigecycline ^b	
<i>Pseudomonas aeruginosa</i>	PIP-TZ Ceftazidime/cefepime IMP/MERO Aminoglycosides	FQ (↑ resistance) Aztreonam	Combination therapy for serious infections
Anaerobes			
<i>Bacteroides fragilis</i>	Metronidazole	Cefoxitin Carbapenems, BL/BLI Tigecycline	Clindamycin ^a Cefotetan ^a
<i>Clostridium perfringens</i>	Penicillin G ± clindamycin	Doxycycline	Cefoxitin, cefazolin Erythromycin BL/BLI
<i>Clostridium difficile</i>	Metronidazole	Vancomycin (oral)	Fidaxomicin, rifaximin

AP Pen, antipseudomonal penicillin; APAG, antipseudomonal aminoglycoside (amikacin, tobramycin, gentamicin); BL/BLI, β -lactam/ β -lactamase inhibitors (ampicillin-sulbactam [AMP-SB], piperacillin-tazobactam [PIP-TZ], ticarcillin-clavulanate [TC-CL]); CEPH 1/2, first- and second-generation cephalosporins; CEPH 3/4, third- and fourth-generation cephalosporins; clinda, clindamycin; FQ, fluoroquinolones (moxifloxacin, levofloxacin, ciprofloxacin); gent, gentamicin; IMP, imipenem; MERO, meropenem; TMP/SMX, trimethoprim/sulfamethoxazole.

^aSelect organisms with published increasing resistance.

^bActivity demonstrated in a few published studies; not FDA-approved for this indication.

them. Additionally, alternative therapy, secondary options, and selected therapy for multidrug-resistant (MDR) organisms are included.

Antimicrobial Combination

Single agents can treat many infections. However, in certain circumstances, antimicrobial combinations can be considered. When antimicrobial agents are combined, the interactions exhibited against an organism in vitro can be indifference, synergism, or antagonism.

Several circumstances in the critical care setting for which combination antimicrobials might be appropriate include the following:

- Initial therapy in immunocompromised/critically ill patients, for example, neutropenic fevers when the initial nature of the infection is unclear.
- Critically ill patients with suspected sepsis of an unknown source need to be empirically covered with broad-spectrum drugs to cover methicillin-resistant *Staphylococcus aureus* (MRSA), resistant gram-negative rods (GNR), and possible anaerobes.
- Polymicrobial infections: a mix of aerobic and anaerobic organisms requiring broad coverage often causes

intra-abdominal, pelvic, and diabetic foot infections. Antibiotics such as carbapenems, β -lactamases, and β -lactamase inhibitors provide broad coverage that can be utilized as monotherapy.^{29,30}

- Synergism: Use of combination antimicrobials has proven synergistic only in limited clinical settings.^{31,32} An example is the use of the combination of penicillin and aminoglycosides for the treatment of enterococcal endocarditis, which results in cure rates comparable to those achieved for endocarditis caused by less resistant streptococci. Similarly, synergistic combination therapy may be useful in the treatment of infections with *S. viridans*, *S. aureus*, and *P. aeruginosa*.

Although the use of antimicrobial combinations may be beneficial, inappropriate use can result in adverse events that include antagonism, increased cost, side effects, and the emergence of resistant organisms.

Antimicrobial Resistance in Critical Care

Currently, antimicrobial resistance is becoming more prevalent while antimicrobial development is relatively stagnant. This phenomenon has been shown to lead to increased morbidity and mortality, higher risk of severe infections, longer

hospital stays, and increased costs.^{33,34} It is therefore important that healthcare providers learn how to achieve clinical efficacy without further compromising the existing antibiotic armamentarium.

Bacterial resistance of antimicrobials occurs mainly through four mechanisms: altered uptake due to decreased permeability, increased efflux, target modification, and hydrolysis or modification of the antibacterial agent (most predominant mechanism).

The emergence of resistance and spread of resistant microorganisms in critical care units are dependent on several factors, including the propensity of the microorganism to acquire resistance, the presence of human and inanimate reservoirs in which resistant organisms can survive, and existing institutional strategies for use of antimicrobial agents. The emergent nature of care, prolonged hospital stays, use of invasive devices, prior antibiotic use, and the increasing presence of chronically ill patients in critical care units have also played a significant role. Additionally, transmission of resistant organisms often occurs among the debilitated and elderly inmates of long-term care facilities. When these colonized patients fall ill, they are often admitted to ICUs, where they are responsible for further spreading antimicrobial resistance.

Emergence of resistant GNRs—extended-spectrum β -lactamase (ESBLs) and carbapenemase-resistant Enterobacteriaceae (CREs)—has become a threat to global health. Therapy of these organisms is challenging due to widespread resistance to current antibiotics and has been associated with increased mortality and prolonged hospitalization.

ESBLs are enzymes that confer resistance to most β -lactam antibiotics, including penicillins, cephalosporins, and aztreonam.³⁴ ESBL-producing Enterobacteriaceae are prevalent both in community and hospital settings and infections with such organisms. Generally, carbapenems are the best antimicrobial agents for infections caused by such organisms³⁵ (Table 44-2).

CREs are gram-negative pathogens that can produce carbapenem-hydrolyzing β -lactamase (CREs). The emergence of these enzymes has threatened the clinical utility of the carbapenem class.³⁶ The development of this resistance is clinically translated into “extreme drug resistance” in gram-negative bacilli, and significantly narrows the choices of effective antimicrobial therapy. Polymyxins are the best agents for such infections. Aminoglycosides and tigecycline may have some activity (Table 44-2). Risk factors for colonization with CRE include recent antibiotic exposure, renal disease, altered levels of consciousness, immunosuppression, diabetes mellitus, vascular disease, and indwelling devices.³⁷

Several strategies have been utilized to prevent the spread of resistant:

- Hand washing, protective barriers, and educational programs for healthcare workers
- Patient isolation and use of dedicated equipment in patients with resistant organisms
- Use of surveillance cultures and antimicrobial resistance surveillance in critical care

- Early and prompt diagnosis of infections
- Appropriate antibiotic use with targeted empirical therapy and knowledge of local antibiograms
- Antimicrobial stewardship to curtail emergence of resistance

The features of antimicrobial stewardship^{7,37,38} are as follows:

- Prospective audits with intervention and feedback
- Formulary restriction and preauthorization
- Clinical pathways and guidelines
- Dose optimization
- Combination therapy guidelines
- Streamlining and de-escalating/tailoring therapy
- Antimicrobial cycling and switching
- Parenteral to oral conversion as soon as possible

Optimal Duration of Antimicrobial Therapy

Longer duration of antimicrobials can be associated with increased rates of adverse events, including *Clostridium difficile*-associated diarrhea, bacterial resistance due to selective pressure, and higher costs of treatment. There has been a trend toward decreasing days of antibiotic treatment for several commonly encountered infections while keeping adverse outcomes such as relapse of infection or mortality rates low. Widely accepted treatment guidelines are still typically followed for conditions such as osteomyelitis and endocarditis. Some conditions may be able to be adequately treated with short courses of antibiotics:

- A review of clinical trials investigating optimal length of treatment for intra-abdominal infections showed comparable clinical cure rates when 5 to 14 days of antibiotics were given. The majority of studies looked at secondary peritonitis with good source control.³⁹
- A meta-analysis looking at treatment duration for VAP showed that short (7–8 days) versus long (10–15) days yielded no differences in 28-day mortality, duration of mechanical ventilation, ventilator-free days, or length of ICU stay.⁴⁰
- Clinical and microbiological failure rates were not significantly different when ≤ 7 , or 10- to 14-day treatment courses were used to treat pyelonephritis and UTIs complicated by sepsis in a review and meta-analysis, including 8 randomized controlled trials (RCTs).⁴¹

Antimicrobial Prophylaxis for Surgical Procedures

A recent consensus statement by the American Society of Health-System Pharmacists (ASHP), the Infectious Diseases Society of America (IDSA), the Surgical Infection Society (SIS), and the Society for Healthcare Epidemiology of America (SHEA) has provided guidelines for antimicrobial prophylaxis.⁴²

TABLE 44-3: Antimicrobial Prophylaxis by Procedure and Likely Infecting Organisms^{40,41}

Type of Procedure	Typical Microbiologic Flora at the Site	Recommended	Alternate
Cardiovascular/thoracic	<i>S. aureus</i> , CoNS	Cefazolin or cefuroxime	Vancomycin
Gastroduodenal/biliary	GNR, streptococci, oropharyngeal anaerobes	Cefazolin, cefoxitin, cefuroxime, or cefotetan	Ampicillin-sulbactam TC-CL
Colonic	GNR, anaerobes	Oral: neomycin + erythromycin or metronidazole Intravenous: cefoxitin or cefazolin + metronidazole	Clindamycin or metronidazole + ciprofloxacin or aztreonam
Head and neck	<i>S. aureus</i> , streptococci, oropharyngeal anaerobes	Cefazolin or clindamycin	Addition of gentamicin controversial
Neurosurgical	<i>S. aureus</i> , CoNS	Cefazolin or clindamycin	Vancomycin
Obstetrics/gynecologic	GNR, enterococci, group B streptococci, anaerobes	Cefazolin, cefoxitin, cefotetan, or cefuroxime PCN G or cefazolin	Ampicillin-sulbactam Doxycycline
• Hysterectomy			
• C-section			
• Abortion			
Orthopedic	<i>S. aureus</i> , CoNS, streptococci, GNR	Cefazolin or ceftriaxone Addition of GNR coverage such as gentamicin	Vancomycin
Urologic (preoperative bacteriuria)	GNR	Cefazolin followed by nitrofurantoin or TMP/SMX	

Based on their recommendations, the key points in selecting appropriate prophylactic therapy include the following:

- Type of procedure (Table 44-3)^{43,44}
- Coverage against expected flora (Table 44-3)
- Commonly encountered microbial flora
- Patient's history of resistant organisms
- Local resistance patterns
- Allergies
- Organ dysfunction
- Penetration of antibiotic into the required site
- Risk factors for acquisition of resistant pathogens
- Weight based dosing: PK properties such as high BMI can lower the drug concentration in the tissue and can increase the risk of surgical site infections.

Many environmental factors also must be taken into account, such as basic infection control procedures, the duration of surgery, and surgical techniques. Current guidelines recommend administering antibiotics within 60 minutes prior to time of surgery. Some antibiotics (e.g., quinolones, vancomycin) require longer infusion times; thus, their doses may be started up to 120 minutes before the first incision.

For most surgical procedures, a single dose may be sufficient; several commonly used antibiotics have half-lives that require supplemental administrations during longer surgeries. In general, if the procedure is continuing beyond 2 half-lives of the antibiotic, it should be administered again intraoperatively.

Antivirals in Critical Care

Viral infections are more commonly seen in patients with acquired immune deficiency syndrome (AIDS) and

neutropenia, and in patients in immunocompromised states. During winter months, severe episodes of influenza can result in respiratory failure and may require admission to a critical care unit. Neuraminidase inhibitors such as oseltamivir are commonly used to treat influenza, and have shown benefit in critically ill patients with influenza A when treatment is started within two days of symptom onset.⁴⁵ In the last few decades, there have been remarkable advances in antiviral therapy. Prior to the 1970s, a diagnosis of a severe viral infection was treated largely with supportive care. Today, there are several treatment alternatives for some viral infections, as shown in Table 44-4.²⁸

Antifungal Therapy in Critical Care

In the last two decades, fungal diseases have become progressively more important in critically ill patients. Immunocompromised patients with serious fungal infections often require critical care; patients in critical care settings are often susceptible to these infections.

In the past decade, the rate of hospital-acquired fungal infection has nearly doubled, with the greatest increase in critically ill surgical patients.⁴⁶

Several factors have been identified as independent predictors for invasive fungal complications during critical illness.⁴⁷⁻⁵⁰ They include:

- Duration of ICU care and invasive mechanical ventilation
- Diabetes mellitus
- Neutropenia
- Organ transplantation and immunosuppression
- Solid and hematologic malignant tumors

 **TABLE 44-4: Spectrum of Selected Antivirals in Critical Care with Permission²⁸**

	HSV-1	HSV-2	CMV	VZV	EBV	Flu A	Flu B	RSV	Adenovirus
Acyclovir/famciclovir/ valacyclovir	+++ ^a	+++ ^a	+/- ^a	+++ ^a	+	0	0	0	0
Ganciclovir/valganciclovir	++	++	+++ ^a	+	++	0	0	0	+/-
Cidofovir	++	++	+++	+	++	0	0	0	+
Foscarnet	++	++	+++	++	++	0	0	0	0
Ribavirin	0	0	0	0	0	0	0	1	0
Oseltamivir/zanamivir	0	0	0	0	0	++ ^a	++ ^a	0	0

Flu, influenza; 0, no activity; +/-, possible activity; + + +, first-line activity; + +, second-line activity; +, third-line (least active).
^aResistant strains reported.

- Long-term use of central venous catheters and urinary catheters
- *Candida* colonization
- Use of broad-spectrum antibiotics
- Use of corticosteroids
- Total parenteral nutrition (TPN)
- Burns
- GI surgery

The major pathogenic fungal organisms encountered in critical care are *Candida albicans* (59% of candidal isolates),

Candida glabrata, other non-albicans *Candida* species, *Aspergillus*, and other emerging fungal organisms, such as zycomycetes.^{47,50}

Fungal therapy is usually used in four different settings in the ICU: prophylactic, preemptive, empirical, and definitive. Prophylactic therapy is hardly employed in critical care except in high-risk patients such as neutropenic patients, bone marrow patients, or solid organ transplant patients.^{50,51} Preemptive therapy is used rarely and involves the treatment of patients at high risk of developing deep candidiasis identified by clinical or laboratory markers. These could include patients with severe burns, patients on extracorporeal

 **TABLE 44-5: Selected Antifungals in Critical Care with Permission²⁸**

Antifungal Agent	Indications for Use	Special Comments
Fluconazole	+++ : <i>C. albicans</i> , <i>C. tropicalis</i> , <i>C. parapsilosis</i> , <i>C. guilliermondi</i> + : <i>C. lusitaniae</i> ± : <i>C. glabrata</i> Fungistatic to <i>Aspergillus</i> , coccidiomycosis, cryptococcus, blastomycosis, histoplasmosis, <i>Sporothrix</i>	No activity against <i>C. krusei</i> , <i>Aspergillus</i> , fusarium, <i>Scedosporium</i>
Voriconazole	+++ : <i>C. albicans</i> , <i>C. parapsilosis</i> , <i>C. tropicalis</i> , <i>C. guilliermondi</i> ++ : <i>C. krusei</i> , <i>C. lusitaniae</i> + : <i>C. glabrata</i> <i>Aspergillus</i> , fusarium, <i>Scedosporium</i> , dermaticeous molds, coccidiomycosis, cryptococcus, blastomycosis, histoplasmosis, <i>Sporothrix</i>	No activity against zycomycetes (mucor, rhizopus, and so on)
Posaconazole	+++ : <i>C. albicans</i> , <i>C. parapsilosis</i> , <i>C. tropicalis</i> , <i>C. guilliermondi</i> ++ : <i>C. krusei</i> , <i>C. lusitaniae</i> + : <i>C. glabrata</i> <i>Aspergillus</i> , fusarium, <i>Scedosporium</i> , dermaticeous molds, zycomycetes, coccidiomycosis, cryptococcus, blastomycosis, histoplasmosis, <i>Sporothrix</i>	Liquid formulation that has to be taken with fatty meals
Caspofungin Micafungin Anidulafungin	<i>C. albicans</i> , <i>C. parapsilosis</i> , ^a <i>C. glabrata</i> , <i>C. tropicalis</i> , <i>C. krusei</i> , <i>C. lusitaniae</i> , <i>C. guilliermondi</i> ^a	Case reports of combination therapy with polyenes against mold infections
Amphotericin B <ul style="list-style-type: none">• Standard• Lipid complex• Liposomal	<i>C. albicans</i> , <i>C. parapsilosis</i> , <i>C. glabrata</i> , <i>C. tropicalis</i> , <i>C. krusei</i> , <i>C. lusitaniae</i> , <i>C. guilliermondi</i> <i>Aspergillus</i> , fusarium, zycomycetes, coccidiomycosis, cryptococcus, blastomycosis, histoplasmosis, <i>Sporothrix</i>	More nephrotoxicity with standard formulation No activity against <i>Aspergillus terreus</i> spp.

+++ , higher activity; ++ , active (second line); + , least active (third line); ± , possible activity.
^aHigher MIC.

membrane oxygenation systems or left-ventricular assist devices, or patients with pancreatitis.⁵²

Empirical therapy is used in the treatment of patients suspected to have deep candidiasis without microbiologic, histologic, or serologic confirmation, while definitive therapy is the treatment of established deep candidiasis. Table 44-5 is a list of available antifungal agents.²⁸

In summary, antimicrobials remain a crucial part of the armamentarium of drugs in critically ill patients. The judicious use of these drugs is essential not only for good patient outcomes but also for prevention of antimicrobial resistance.

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Sepsis and Septic Shock

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INTRODUCTION

Since the days of Hippocrates, infection has been a leading cause of death. Major scientific discoveries and the findings of medical research have shaped the way we think about and manage infections. Severe sepsis and septic shock remain a major healthcare challenge worldwide, affecting an estimated 56 to 91 out of every 100,000 individuals. Of the 120 million patients presenting to United States (US) emergency departments (EDs) each year, 2.9% or over 600,000 are diagnosed with severe sepsis or septic shock. Sepsis is responsible for 9% of all deaths in the United States each year—a total of approximately 210,000 fatalities. By comparison, only 180,000 people die of acute myocardial infarction (MI) and only 200,000 of lung or breast cancer annually. With healthcare costs in the United States totaling \$387 billion in 2011, septicemia was the most expensive admission diagnosis, at a cost of over \$20.3 billion, or 5.2% of the total aggregate cost of all hospitalizations. Historically, hospital mortality for sepsis, severe sepsis, and septic shock has been 15%, 20%, and 47%, respectively.¹⁻⁴ Since the advent of the Surviving Sepsis Campaign (SSC), sepsis mortality decreased from 35% to 15.4% in Australia and New Zealand, and from over 45% to 25% in the United Kingdom.⁵⁻¹⁰ Increased compliance with quality improvement measures and sepsis initiatives have resulted in similar mortality risk reductions in the United States. During a 7.5-year study period, a 25% reduction was observed.¹¹

In countries without sepsis quality initiatives, mortality for severe sepsis and septic shock is reported between 22% and 76%.^{12,13}

The ED is the portal of entry for over 50% of septic patients admitted to US hospitals.^{14,15} Detection of sepsis in the early phase has been shown to be crucial to preventing disease progression and improving outcomes.

Risk factors and comorbidities associated with the increased incidence and mortality in severe sepsis and septic shock include age, gender, race, multidrug-resistant organisms, and severity of chronic illnesses.¹⁶ Elderly patients are most severely affected by this disease. The estimated incidence of sepsis in patients over 85 years of age is 26.2/1,000 versus 0.2/1,000 in children.¹⁷ Patients with suspected sepsis had a mean ED length of stay (LOS) of 4.7 hours, with approximately 20.4% of patients staying longer than 6 hours.³ For these reasons, the emphasis on improving ED management of sepsis has been a revolutionary approach to decreasing morbidity and mortality from this disease.

THE DEFINITION OF SEPSIS

A 1992 Consensus Conference provided a definition of sepsis as “suspected or known infection with two or more systemic inflammatory response criteria,” and defined a systemic inflammatory response syndrome (SIRS) as “a physiological

**TABLE 45-1: Summary of Definitions****Infection**

Defined as a pathologic process caused by the invasion of normally sterile tissue, fluid, or body cavity by pathogenic microorganisms.

Systemic inflammatory response syndrome (SIRS)

Defined as a physiologic response to an inflammatory process from a variety of severe clinical insults, manifested by at least two or more of the following:

1. Temperature $> 38^{\circ}\text{C}$ or $< 36^{\circ}\text{C}$
2. Heart rate > 90 beat/min
3. Respiratory rate > 20 breaths/min or $\text{Paco}_2 < 32$ mm Hg
4. WBC count $> 12,000$ or $< 4,000/\text{mm}^3$ or $> 10\%$ immature (band) forms

Sepsis

Sepsis is a systemic inflammatory response to an infection, defined as at least two SIRS conditions as a result of infection.

Severe sepsis

Defined as acute sepsis-induced organ dysfunction, hypoperfusion (lactic acidosis, oliguria, or mental status alteration), or hypotension.

Septic shock

Defined as sepsis-induced persistent hypotension, despite adequate fluid resuscitation, along with the presence of perfusion abnormalities, which may include, but are not limited to, lactic acidosis, oliguria, and mental status alteration.

response to an inflammatory process arising from nonspecific insult as seen in a variety of infectious or noninfectious processes such as infection, pancreatitis, trauma, burn and other diseases.” The conference described SIRS as a continuum, worsening and evolving to sepsis, severe sepsis, and septic shock (Tables 45-1 and 45-2).¹⁸ The first novel use of SIRS criteria in the ED revealed a positive correlation between the number of SIRS criteria, ED LOS, probability of admission, length of hospital stay, and hospital costs.¹⁵

SURVIVING SEPSIS CAMPAIGN

The SSC was initiated to increase the awareness of sepsis, severe sepsis, and septic shock, to increase the likelihood of early and accurate diagnosis, and to improve the processes of care in the monitoring and treatment of septic patients in the ED. The goal was to improve mortality through an international standardization of screening, treatment, and quality process improvement programs involving a three-phase approach.

In phase I, the goal was to establish the baseline physician and public awareness of severe sepsis and septic shock. This phase created a system of global accountability announced during the European Society of Intensive Care meeting in Barcelona, Spain, October 2002. An international survey of 1,058 physicians from 6 countries was conducted, with respondents categorized as either “intensivist” (50% clinical time in an adult ICU) or “other” (10% clinical time in an

**TABLE 45-2: Diagnostic Criteria for Sepsis**

Infection,^a documented or suspected, and some of the following:

General variables

- Fever (core temperature $> 38.3^{\circ}\text{C}$)
- Hypothermia (core temperature $< 36^{\circ}\text{C}$)
- Heart rate $> 90/\text{min}$ or > 2 SD above the normal value for age
- Tachypnea
- Altered mental status
- Significant edema or positive fluid balance (> 20 mL/kg over 24 h)
- Hyperglycemia (plasma glucose > 120 mg/dL or 7.7 mmol/L) in the absence of diabetes

Inflammatory and hematologic variables

- Leukocytosis (WBC count $> 12,000/\mu\text{L}$)
- Leukopenia (WBC count $< 4,000/\mu\text{L}$)
- Normal WBC count with $> 10\%$ immature forms
- Döhle’s bodies, toxic granulation, and vacuoles
- Plasma C-reactive protein > 2 SD above the normal value
- Plasma procalcitonin > 2 SD above the normal value
- Hemoconcentration (dehydration)
- Thrombocytopenia
- Fibrin degradation products

Hemodynamic variables

- Arterial hypotension (SBP < 90 mm Hg, MAP < 70 mm Hg, or an SBP decrease > 40 mm Hg in adults or > 2 SD below normal for age)
- Mixed venous oxygen saturation ($\text{SvO}_2 < 70\%$)
- Cardiac index < 3.5 L/min/m

Organ dysfunction variables

- Arterial hypoxemia ($\text{Pao}_2/\text{FiO}_2 < 300$)
- Acute oliguria (urine output < 0.5 mL/kg/h or 45 mmol/L for at least 2 h)
- Creatinine increase > 0.5 mg/dL
- Coagulation abnormalities (INR > 1.5 or aPTT > 60 s)
- Ileus (absent bowel sounds)
- Thrombocytopenia (platelet count $< 100,000/\mu\text{L}$)
- Hyperbilirubinemia (plasma total bilirubin > 4 mg/dL or 70 mmol/L)

Tissue perfusion variables

- Hyperlactatemia (> 2 mmol/L)
- Decreased capillary refill or mottling

SD, standard deviation; WBC, white blood cell; SBP, systolic blood pressure; MAP, mean arterial blood pressure; SvO_2 , mixed venous oxygen saturation; INR, international normalized ratio; aPTT, activated partial thromboplastin time.

^aInfection defined as a pathologic process induced by a microorganism.

adult ICU), of whom emergency physicians composed 23% ($n = 119$). A total of 68% of respondents were concerned about the lack of a common definition of sepsis. Of respondents concerned about the absence of a common definition, 83% stated that this may result in missed diagnosis. Less than 17% of physicians agreed on a common definition of sepsis, despite the publication of definitions in the 1992 American College of Chest Physicians and Society of Critical Care Medicine Sepsis Definitions Consensus Statement, published in 2000, two years before the survey was conducted.^{18,19}

In phase II, representatives from 11 international medical professional organizations reviewed the literature pertaining to severe sepsis and septic shock management. The goal was to provide guidelines that would be of practical use to the physician practicing at the bedside. The representatives agreed on a series of recommendations from the acute to the subacute management of this disease process. The American College of Emergency Physicians (ACEP) contributed significantly to the process of guideline development through the representation and engagement of ACEP's Clinical Policies Committee. A full 75% of the revisions and content that ACEP considered moderately important and 100% of those that ACEP considered of major importance were incorporated into the final version of the guidelines.²⁰

The guideline methodology and content continue to improve over time due to the Grading of Recommendation Assessment, Development and Evaluation (GRADE), a system used to guide and evaluate the quality of evidence based on sequential evaluation and ranking from high, or Class A evidence (i.e., a randomized control trial), to very low, or Class D evidence (i.e., downgraded controlled studies or expert opinion based on other evidence). The system also classifies recommendations as strong, assigning a grade of 1, or weak, assigning a grade of 2. Each trial can be upgraded to a higher level of evidence or downgraded to a lower level of evidence based on its limitations, inconsistencies, or an impression of the results. Thus, the highest possible recommendation would be 1A.²⁰

The SSC and collaborators recognized that a focused implementation plan would be required to demonstrate measurable improvements in severe sepsis and septic shock outcomes. To assist in accomplishing this goal, the SSC formed a partnership with the Institute for Healthcare Improvement, a nonprofit organization dedicated to accelerating the improvement of healthcare by advancing the quality and value of healthcare resources.

The two organizations worked together to incorporate "treatment bundles" for the management of severe sepsis and septic shock. A treatment bundle is a group of interventions that, when administered together, may be more efficacious than when administered individually. A treatment bundle, as defined by the Institute for Healthcare Improvement, incorporates a few key elements from the guidelines that, when combined and performed within the same time and space, act synergistically, generating improved outcomes.

In phase III, updates to the guidelines and management of severe sepsis and septic shock were published in 2004, 2008, and 2013.^{20–22} This chapter will review the recommendations from the international guidelines for severe sepsis and septic shock from 2012. However, guideline revisions are currently commencing and are expected to be published in 2016. Some of the recommendations in this chapter are preceding those guidelines, but may not be endorsed by the SSC at this time.

THE PATHOGENESIS OF SEPSIS

While the complete pathogenesis of sepsis is yet to be unraveled, it is hypothesized that infection results in a variable

host response that is comprised of an intricate series of reactions in which both proinflammatory and anti-inflammatory pathways play key roles. These pro- and anti-inflammatory pathways can facilitate clearing of the infection and promotion of tissue recovery, but can also cause an overwhelming response that may result in organ injury and secondary infection, depending on the virulence of the pathogen and the preexisting medical condition of the patient.²³

Innate immunity is the first line of defense against pathogenic challenge. It is comprised of a series of reactions that recognize and activate the immune response. This response can be initiated by four major receptors types: toll-like receptors, C-type lectin receptors, retinoic acid-inducible gene-1-like receptors, and nucleotide binding oligomerization domain-like receptors. Activation of these receptors causes tissue damage and necrotic cell death, which results in the release of damage-associated molecular pattern molecules, so-called danger molecules. These reactions cause coagulation impairment that can lead to disseminated intravascular coagulation (DIC), microvascular thrombosis, loss of barrier function by capillary leakage, interstitial edema, and vasodilatation, which, in turn, produces the tissue hypoperfusion and tissue hypoxia that cause oxidative stress. Oxidative stress results in mitochondrial damage and creates an imbalance between oxygen delivery and oxygen consumption, thus producing an oxygen debt.²⁴

Animal and human models of early sepsis have repeatedly shown that circulatory insufficiency generates an imbalance between systemic oxygen delivery (DO_2) and demand, creating global tissue hypoxia (shock), and oxygen debt accumulation. Thus, circulatory insufficiency is a combination of hypovolemia, loss of vasomotor tone, myocardial depression, increased metabolic demands, multiorgan dysfunction (i.e., hypoxia-acute lung injury) and microcirculatory or mitochondrial derangements.^{24–26} Circulatory insufficiency can be more objectively described and quantitated from an oxygen transport and utilization perspective.

A critical decrease in DO_2 is followed by an increase in the systemic oxygen extraction ratio (OER) and a decrease in central venous (ScvO_2) or mixed venous oxygen saturation (SvO_2).²⁷ This increase in the OER is a compensatory mechanism to match systemic oxygen demand, and is associated with increased mortality.^{27–29} Anaerobic metabolism ensues when the limit of this compensatory mechanism (oxygen extraction ratio > 50%) is reached, leading to lactate production.³⁰ In this critical DO_2 -dependent phase, lactate concentrations are inversely related to DO_2 and $\text{ScvO}_2/\text{SvO}_2$.²⁵

RISK STRATIFICATION

In the transition from SIRS to severe disease, early cardiovascular insufficiency is the most significant organ dysfunction that is associated with increased morbidity and mortality.^{31–34} Thus, the addition of hypotension and elevated serum lactate level to SIRS criteria improves risk stratification and detects those patients at risk for sudden cardiopulmonary decompensation. Early risk stratification has independently changed

the clinical and hemodynamic phenotype and mortality of sepsis over the last two decades. The mortality reduction attributed to simply measuring a lactate level within 6 hours is estimated to be 12.1% to 21.4%. This mortality may be partly related to a 50% reduction in sudden cardiopulmonary complications.^{35–43}

Lactate is a marker for global tissue hypoxia, a byproduct of anaerobic metabolism when the oxygen delivery is insufficient to meet oxygen demand. Several studies have shown that lactate levels above 4 mmol/L are associated with increased mortality in trauma, postoperative, and sepsis patients.^{31–33} In certain patient populations with severe sepsis and septic shock, there is a delayed or absent elevation of lactate levels despite hypotension. Thus, elevated lactate levels are helpful when present, but not helpful when absent.

BIOMARKERS AND DIAGNOSTICS IN SEPSIS

Biomarkers as diagnostic, therapeutic, and prognostic tools in sepsis continue to evolve. Other markers have shown promise, but all lack sensitivity and specificity to detect patients in the early phase of sepsis and septic shock. While procalcitonin (PCT) and C-reactive protein (CRP) have been used to differentiate sepsis from other inflammatory causes, the lack of evidence at this time precludes recommending these biomarkers alone, but rather in conjunction with other diagnostic tools.

SCREENING AND IDENTIFICATION FOR SEPSIS

Sepsis is a time-sensitive diagnosis; reducing the progression to severe sepsis and septic shock through early identification and intervention has been shown to play a critical role in decreasing mortality. For a successful screening process to work, ongoing education and awareness is crucial. The SSC website provides several examples of validated screening tools.⁴⁴

Sepsis Bundles

Sepsis bundles were derived in order to facilitate care based on the most recent evidence. Originating with the Institute of Healthcare Improvement, care bundles have been adopted by the Centers for Medicare and Medicaid Services (CMS). The CMS guidelines include a 3-hour and 6-hour bundle (Table 45-3).

The 3-hour bundle includes early identification of sepsis, early broad-spectrum antibiotics and cultures, early lactate measurement, and early intravenous fluids (30 mL/kg of crystalloid for hypotension or lactate ≥ 4 mmol/L).

The 6-hour bundle includes intravascular volume and perfusion assessment, more volume for persistent hypovolemia after intravascular assessment, vasopressors for persistent shock, and repeat lactate measurement.



TABLE 45-3: Surviving Sepsis Campaign Guidelines for Initial Resuscitation¹¹

To be Completed within 3 Hours of Time of Presentation^a

1. Measure lactate level.
2. Obtain blood cultures prior to administration of antibiotics.
3. Administer broad-spectrum antibiotics.
4. Administer 30 mL/kg crystalloid for hypotension or lactate ≥ 4 mmol/L.

To be Completed with 6 Hours

1. Apply vasopressors (for hypotension that does not respond to initial fluid resuscitation) to maintain a mean arterial pressure (MAP) ≥ 65 mm Hg.
2. In the event of persistent hypotension after initial fluid administration (MAP < 65 mm Hg) or if initial lactate was ≥ 4 mmol/L, reassess volume status and tissue perfusion.
3. Remeasure lactate if initial lactate elevated.

^a“Time of presentation” is defined as the time of triage in the emergency department or, if presenting from another care venue, from the earliest chart annotation consistent with all elements of severe sepsis or septic shock ascertained through chart review.

ANTIBIOTICS AND SOURCE CONTROL

Antibiotic therapy remains the cornerstone of treatment for severe sepsis and septic shock. The goal is to start the appropriate empiric therapy, which includes broad-spectrum antibiotics directed against the most likely pathogens.²² Timely administration of appropriately selected antibiotics has significant outcome implications (Table 45-4). Failure to initiate antibiotics prior to or within the first hour of onset of hypotension is associated with a 7.6% increased mortality for each hour that antibiotic delivery is delayed.⁴⁵ The SSC guidelines recommend administration of intravenous (IV) broad-spectrum antibiotics be initiated within the first hour of recognition of severe sepsis and septic shock.²²

Blood and other appropriate cultures should be obtained prior to the initiation of antimicrobial therapy, if such cultures do not cause a significant delay in antibiotic initiation. The current guidelines recommend obtaining cultures to optimize the identification of causative organisms. They recommend obtaining at least two sets of blood cultures (both aerobic and anaerobic bottles), with at least one drawn percutaneously and one drawn through each vascular access site (such as a central line or a PICC line) if those lines were placed more than 48 hours prior to patient presentation. If cultures have not been obtained within the first hour of the onset of septic shock, consideration should be given to starting empiric antibiotic treatment without them. Cultures should then be obtained as soon as possible. Given that intravenous (IV) antibiotics require vascular access, it would seem reasonable that at least one set of blood cultures could be obtained prior to antibiotic infusion.

The most common causes of sepsis are pneumonia (47%), intra-abdominal processes (18%), urinary tract infection (UTI)

TABLE 45-4: Antibiotic Choice^{24–33}

Site	Organism	Antibiotic
Pneumonia: nosocomial	1. Enterobacter 2. <i>Pseudomonas aeruginosa</i> 3. <i>Staphylococcus aureus</i>	1. β -Lactam 2. Add aminoglycoside. 3. Add linezolid if suspect MRSA.
Pneumonia: community acquired	1. <i>S. aureus</i> 2. <i>Streptococcus pneumoniae</i> 3. Gram-negative	Third-generation cephalosporin or macrolide
Urinary tract infection	1. Enterobacteriaceae (<i>Escherichia coli</i>) 2. <i>P. aeruginosa</i> 3. <i>Enterococcus</i> sp.	1. Ciprofloxacin 2. Ceftriaxone or ceftazidime 3. May add aminoglycoside.
Abdominal source	1. Gram-negative bacilli (<i>E. coli</i> , <i>P. aeruginosa</i>) 2. Gram-positive cocci (<i>Enterococcus</i> sp.) 3. Anaerobes (<i>Bacteroides</i> sp.)	1. Piperacillin–tazobactam 2. Ceftriaxone, ceftazidime, or cefepime plus metronidazole 3. Imipenem, with fluconazole and aminoglycoside
Skin source	1. <i>Streptococcus</i> sp. 2. <i>Staphylococcus</i> sp. 3. Anaerobes	1. β -Lactam/lactamase inhibitor 2. Piperacillin/tazobactam 3. Cefoxitin
Indwelling catheter septicemia	1. <i>Staphylococcus</i> sp. 2. Enterobacteriaceae 3. <i>P. aeruginosa</i>	Linezolid with β -lactam
Meningitis	1. Gram-negative bacilli (<i>Acinetobacter</i> sp.) 2. <i>Staphylococcus</i> sp. 3. <i>Streptococcus</i> sp.	1. Meropenem with glycopeptide 2. Cefotaxime with fosfomycin

Selection depends on each region pattern and it is always best to consult a local antibiogram. The most common causes are given in the table.

(18%), and bloodstream infection (12%). Other sources of infection include skin, nosocomial meningitis, and indwelling catheters.⁴⁶

Source control is strategic in the early management of sepsis. This includes drainage of infected fluids, debridement of infected soft tissues, removal of infected devices or foreign bodies, and, finally, definite measures to correct anatomic derangement resulting from ongoing microbial contamination. A clear diagnostic approach to source identification and eradication should be attempted as soon as possible and within the first 12 hours after the diagnosis is made, if at all feasible.²²

In surgical sepsis, every hour of delay from admission to operation was associated with an adjusted 2.4% decreased probability of survival or a 16% increased mortality if no source control was achieved within 6 hours.^{37–39} Patients who had surgical source control delayed for more than 6 hours had a significantly higher 28-day mortality (42.9% vs. 26.7%, $P < 0.001$); this delay was independently associated with an increased risk of death.³⁷

INITIAL RESUSITATION

Early quantitative resuscitation, as endorsed by the SSC, is a protocol for accomplishing specific clinical endpoints within the first 6 hours of severe sepsis/septic shock presentation. It is intended to restore the balance between oxygen delivery and demand through optimizing preload (volume), afterload

(blood pressure), and contractility (stroke volume) in order to preserve effective tissue perfusion while avoiding excessive increases in myocardial oxygen consumption (i.e., avoiding tachycardia and maintaining coronary perfusion pressure) and fluid overload. This involves optimizing preload for hypovolemia, mean arterial pressure (MAP) with vasopressors if the MAP remained low after volume administration, ScvO₂ with supplemental oxygen and packed red blood cells (PRBC) as indicated, using inotropic agents if necessary (dobutamine), and decreasing systemic oxygen demands (mechanical ventilation).

The early goal-directed therapy (EGDT) study was a single-center, partially blinded (90%, all ICU care) randomized controlled trial (RCT) that reported a 15.9% and 12.6% absolute reduction in 28- and 60-day mortality, respectively, in the EGDT group. The trial was stopped early by the Data Safety and Monitoring Committee due to safety concerns for the standard-of-care group. Not only was mortality decreased in the EGDT group for the study, the mortality was decreased by 5% over prospectively examined controls prior to the trials' initiation.

Advances

Between 2014 and 2015, three trials were published with similar protocols: ProCESS,⁵⁰ ARISE,⁵¹ and ProMISe.¹⁰ The results of all three trials were consistent. From a population standpoint, if comprehensive processes were in place for



TABLE 45-5: A Comparison of the ProMISe, ARISE and ProCESS Studies

Study	ProMISe		ARISE		ProCESS		
	EGDT	UC	EGDT	UC	EGDT	Protocol Based	UC
Time to identification ^a	96	102	84	78	72	66	69
First antibiotic dose			70	67			
Central Line (%)	92.10	50.90	13.70	61.90	93.60	56.50	57.90
ScvO ₂ central catheter (%)			90.00	0.40	93.20	4.00	3.50
Arterial Line (%)	74.20	62.20	91.4	76.30			

^aTime from ED presentation to meeting inclusion criteria.
Medians given in minutes.

early detection, intravenous fluid administration, antibiotic administration, and lactate measurement, subsequent algorithm-driven EGDT (as defined by the original trial, including continuous central venous oxygenation monitoring)⁴¹ did not lead to an improvement in outcomes (Table 45-5). The possibility that individual elements may be beneficial in specific patient populations remains and requires further evaluation. Any hospital not consistently and effectively employing a protocol for early identification (1–2 hours from triage), early IV fluids (2 L within the first 3 hours), early antibiotics (within the first 1–2 hours from identification), and early lactate measurement may not achieve similar results. An additional difference between these studies and the original EGDT study is that in ProMISe, PROCESS, and ARISE, patients achieved ICU admission within 2 to 3 hours compared to 6 to 8 hours in the EGDT study.

A number of potential reasons for differences in results from the original study exist: randomization occurred later, patients appeared to be less ill at baseline, all patients received antibiotics prior to randomization (Table 45-6), and the potential for a gradual redefining of usual care due to the influences of the original paper⁴¹ and the Surviving Sepsis Guidelines publications.^{20,21} These guidelines emphasized time-dependent identification, fluid therapy, rapid antibiotic administration and early lactate measurement, which are

currently considered standard of care and may have changed the clinical and hemodynamic phenotype of sepsis care. Pre-hospital care, sepsis alerts, rapid response systems, telemedicine, and palliative care are all examples of progress in the care of septic patients since the advent of the SSC.

Initial resuscitation for severe sepsis and septic shock is time and treatment dependent. An international sepsis quality improvement program recently reported the prevalence and mortality of septic patients requiring emergent resuscitation. Severe sepsis patients initially presenting with hypotension alone (MAP < 65 mm Hg), hypotension with hyperlactemia (> 4 mmol/L), or hyperlactemia alone have a significant prevalence and mortality difference²² (Table 45-7). An evaluation of septic patients in England from an ICU case-mix program reported a prevalence of refractory hypotension alone, hyperlactemia with hypotension, and hyperlactemia alone at 18.2%, 44.5%, and 37.3%, respectively.¹⁰ Both evaluations reported elevated mortality in patients with both hypotension and hyperlactemia ranging between 37.3%¹⁰ and 46.1%²². The mortality of hyperlactemia alone (26.2%¹⁰ and 30%²²) and hypotension alone (31.4%¹⁰ and 36.7%²²) were additionally elevated.

Initial resuscitation for severe sepsis and septic shock is time and treatment dependent. Any sepsis quality improvement program should include a process for early identification,



TABLE 45-6: Differences Between the Important Studies of the Treatment of Septic Shock

Study	Rivers		ProMISe		ARISE		ProCESS		
	EGDT	UC	EGDT	UC	EGDT	UC	EGDT	Protocol Based	UC
Time to randomization ^a	1.3	1.5	2.8	2.7	2.8	2.7	3.2	3	3
Antibiotics prior to randomization	No		Yes		Yes		Yes		
APACHE II	20.4	21.4	15.4	15.8	15.4	15.8	20.8	20.6	20.7
Baseline lactate (mmol/L)	7.7	6.9	7.0	6.8	6.7	6.6	4.8	5	4.9
Volume IV fluids (mL)	3499	4981	2226	2022	2515	2591	2805	3285	2279
	± 2938	± 2984	± 1443	± 1271	± 1244	± 1331	± 1957	± 1743	± 1881
Unadjusted mortality	43.3%	56.9%	29.5%	29.2%	18.6%	18.8%	21%	18.2%	18.9%
	(60 Day)	(60 Day)	(90 Day)	(90 Day)	(90 Day)	(90 Day)	(60 Day)	(60 Day)	(60 Day)

^aED presentation to randomization. Median, hours.
EGDT, early goal-directed therapy; UC, usual care.


TABLE 45-7: Mortality Differences Based on Severity at Time of Presentation

	Severe Sepsis Prevalence (%)	Severe Sepsis Mortality (%)
Elevated lactate > 4 mmol/L only	5.9	30.0
Hypotension only; normal lactate	49.5	36.7
Hypotension and an elevated lactate \geq 4 mmol/L	16.6	46.0

Data from Dellinger RP, Levy MM, Rhodes A, et al. Surviving Sepsis Campaign: International guidelines for management of severe sepsis and septic shock: 2012, *Crit Care Med*. 2013 Feb;41(2):580–637.²²

early IV fluid, and antibiotic administration and early lactate measurement.

Based on the results of this trilogy of trials, the initial bundles have been updated by the SSC. A central venous catheter (CVC) does not have to be placed immediately unless peripheral access is unobtainable or vasopressor medication must be initiated. Timely antibiotic administration, fluid resuscitation, and lactate normalization are now the main components of the initial bundle (Table 45-3).

Fluid Therapy

Volume depletion may result from decreased oral intake, increased insensible losses, arterial and venous dilation, and/or transudation of fluid into the extravascular fluid compartment.

Early fluid administration should not be confused with the adverse effects of late or liberal fluid administration in acute lung injury. The Fluids and Catheters Treatment Trial (FACTT) followed patients for 43 hours after being admitted to the ICU and 24 hours after developing a lung injury. The study showed no difference in the 60-day mortality rate.⁵² Conservative fluid management resulted in significantly improved lung function, decreased need for mechanical ventilation, and improvement of central nervous system function secondary to decreased need for sedation in postresuscitation patients.²²

We do suggest that fluid resuscitation be guided by dynamic or static variables, with dynamic being preferred. Potential options for dynamic evaluation such as ultrasound, echocardiography, and bioreactance show promise, although each has strengths and weaknesses. Central venous pressure may not be the best indicator of fluid resuscitation; we recommend using an ultrasound to measure the inferior vena cava index if available in your institution, although this test also has its limitations. (See Chapter 55, Ultrasound Assessment of Fluid Status, for more details.)

Crystalloids are recommended as the first-line agent for resuscitation.²² No specific crystalloid is considered better than another for acute resuscitation, although balanced fluid solutions are preferred in the early phases of evaluation. Fluids are discussed in detail in Chapter 57, Fluid Management. Albumin is recommended as a supplement in patients requiring

substantial amounts of crystalloids.²² A meta-analysis of aggregated data from 17 randomized trials including 1,977 patients reported a survival benefit to albumin-treated septic shock patients when compared to patients receiving any other fluid (odds ratio [OR] = 0.82, 95% confidence interval [CI] = 0.67–1.00; I^2 = 0%). When comparing albumin-treated patients with those receiving crystalloids in seven of the trials totaling 1,441 patients, albumin was again found to be protective (OR = 0.78, 95% CI = 0.62–0.99; I^2 = 0%).⁵³ In ARDS patients, albumin was associated with increased oxygenation without mortality impact.⁵⁴ Two recent meta-analyses report decreased mortality in septic shock patients resuscitated with albumin.^{55,56} However, two other meta-analyses found no difference.^{57–59} We agree with the SSC guidelines of crystalloid solutions, supplemented with albumin if crystalloid resuscitation attempts are unsuccessful.

Hydroxyethyl starches (HES) are not recommended for fluid resuscitation in severe sepsis and septic shock. Studies reported increased mortality and/or an increased need for renal replacement therapy when HES was used. Thus, its use is not recommended until further evidence is available.⁶⁰

EXOGENOUS VASOPRESSORS

In volume-refractory septic shock, vasopressors should be administered to target a MAP goal > 65 mm Hg. Norepinephrine is the first-line agent of choice in septic shock.²² A recent multicenter randomized trial of patients with shock who received dopamine or norepinephrine as a first-line vasopressor to restore or maintain blood pressure noted no significant mortality difference between the two vasopressors. However, dopamine was associated with a greater number of dysrhythmias, especially atrial fibrillation. Thus, norepinephrine is recommended as the first choice in vasopressor therapy.⁶¹ Dopamine predominantly functions as an inotrope.^{62,63} Given that dobutamine use was added blindly to either norepinephrine or dopamine, it is unclear if the proarrhythmic effects were due to the dopamine alone, the combination with a second inotrope, or both. However, due to the proarrhythmic effect of dopamine, it should be considered primarily in bradycardiac patients, those with low inotropic activity, or those with a low threshold for dysrhythmia.

Epinephrine may be added to or substituted for norepinephrine when additional vasopressors are required to maintain adequate blood pressure. Information from four randomized trials (n = 540) comparing norepinephrine to epinephrine found no difference in mortality risk (risk ratio [RR] = 0.96; CI = 0.77–1.21; fixed effect; I^2 = 0%).²² Epinephrine increases lactate levels and may confound the clinical utility of this parameter.

Vasopressin levels in septic shock patients are reported to be lower than in unstressed individuals. Replacement of physiologic vasopressin deficiency has been reported effective in raising blood pressure in this patient population. An RCT comparing norepinephrine alone to norepinephrine plus vasopressin at 0.03 U/min showed no difference in overall mortality. However, in the *a priori* defined subgroups, powered to determine a difference, survival benefit was reported when

vasopressin was administered earlier, in conjunction with lower norepinephrine doses. Additionally, norepinephrine requirements were reduced with vasopressin administration.⁶⁴ In this case, vasopressin is being used as a physiologic replacement, not as a traditional vasopressor. Low-dose vasopressin is not recommended as a single initial agent. High-dose vasopressin (above 0.03–0.04 U/min) should be reserved only as a last resort to achieve the MAP goals in vasopressor (norepinephrine or epinephrine) refractory shock.⁶⁴ Corticosteroids may have a synergistic interaction with norepinephrine and vasopressin. This interaction is associated with improved mortality over norepinephrine and vasopressin alone.⁶⁵

Phenylephrine should be used only as a salvage therapy in patients with refractory shock, as an additional vasopressor in patients who failed to achieve goal MAP, or in patients on norepinephrine with significant tachyarrhythmias. It is recommended that all patients on vasopressors have an arterial line to measure their blood pressure and that vasopressors be administered through a CVC.²² A further summary of vasopressors and inotropes are presented in Chapter 19.

Inotropic Therapy

From a population standpoint, all three contemporary EGDT trials showed no benefit of generalized, protocolized management with dobutamine. From the individual patient level, if one has reason to believe that there is myocardial depression or dysfunction, a focused cardiac assessment with ultrasound should be conducted to assess ventricular function. If it is depressed, dobutamine may be warranted.^{10,50,51}

Blood Product Administration

According to guidelines, a severe sepsis or septic shock patient should receive transfusion of PRBCs when hemoglobin is < 7 g/dL to a target of 7 to 9 g/dL except in patients with significant coronary artery disease, myocardial ischemia, severe hypoxemia, or acute hemorrhage in which a hemoglobin level > 10 g/dL should be maintained.²² In a recently published multicenter randomized trial septic shock patients were transfused at a hemoglobin level of < 7 g/dL in the conservatively treated group and at a hemoglobin level of < 9 g/dL in the liberally treated group. There was no significant mortality difference at 90 days and no increased rate of ischemic events or use of life support between the groups, and less blood transfusion in the < 7 g/dL group.⁶⁶ Of note, the power analysis was based on an estimated 45% mortality, which is significantly higher than any of the trilogy sepsis trials (ProCESS, ProMISe, ARISE) and brings into question both the sample size and result validity. Leading to further debate, another *New England Journal of Medicine* 2015 publication reports a significantly higher mortality with restrictive transfusions in cardiac surgery patients. Survival was higher with Hb > 9 g/dL, which persisted through multiple sensitivity analyses.⁶⁷

In two large randomized trials, the duration of PRBC storage of less than 10 days or less than 7 days versus more than 21 days was not associated with increased mortality or change

in multiple organ dysfunction score (MODS).^{68,69} Fresh frozen plasma should not be transfused to correct coagulopathy unless there is bleeding or a planned invasive procedure. Antithrombin therapy should not be used. Transfuse platelets when the count is < 5,000/mm³ regardless of bleeding, or if the count is 5,000 to 30,000/mm³ with significant bleeding risk.²² More detailed information is available in Chapter 38, Transfusion in Critical Care.

CORTICOSTEROIDS AND THE SEPTIC PATIENT

During the stress of sepsis, the adrenal response may not be sufficient; thus, a relative adrenal insufficiency results, giving rise to adrenal dysfunction. While early studies have shown that steroid replacement has no benefit and may cause harm,⁷⁰ Annane et al. in 2002 showed that replacement of hydrocortisone at 50 mg every 6 hours improved outcomes and decreased vasopressor use.⁷¹ The Corticosteroid Therapy of Septic Shock (CORTICUS) study enrolled a wider population range to investigate this question.⁷² Specifically, patients with systolic blood pressure < 90 mm Hg for 1 hour regardless of vasopressor use, septic shock patients from the ICU up to the first 72 hours, and patients in whom etomidate was used were enrolled. By comparison, Annane et al. enrolled only patients who exhibited persistent hypotension for 1 hour or greater and septic shock patients up to the first 8 hours, and excluded any person in whom etomidate had been used within the previous 6 hours. CORTICUS showed no significant difference in 28-day mortality between corticosteroid and placebo.^{71,72} The exclusion rate was over 50% and the mortality much lower than in the Annane study.

In the latest 2013 guidelines of the SSC, the use of IV hydrocortisone 200 mg/day is recommended for adult patients with persistent septic shock, refractory to fluid therapy and requiring increased vasopressor administration. The guidelines went one step further by making the cosyntropin stimulation test elective and recommending against the use of dexamethasone as a substitute to hydrocortisone.²² Early use of steroids versus late may confer a higher survival rate.⁷³

Activated Protein C

Activated protein C is no longer a component of care for the sepsis patient. This drug was taken off the market and is no longer available as a result of the PROWESS-SHOCK trial, which was stopped mid-study due to no demonstrated benefit in mortality.⁵⁶

SUMMARY

A summary algorithmic approach to septic shock is presented in Figure 45-1.⁷⁴ Early sepsis management is associated with decreased morbidity, mortality, and healthcare resource consumption. Similar to acute MI, stroke, and trauma, the management of sepsis is time-sensitive and requires emergent expertise in the ED. As sepsis has gained the attention of numerous regulatory bodies, quality of care in the ED and

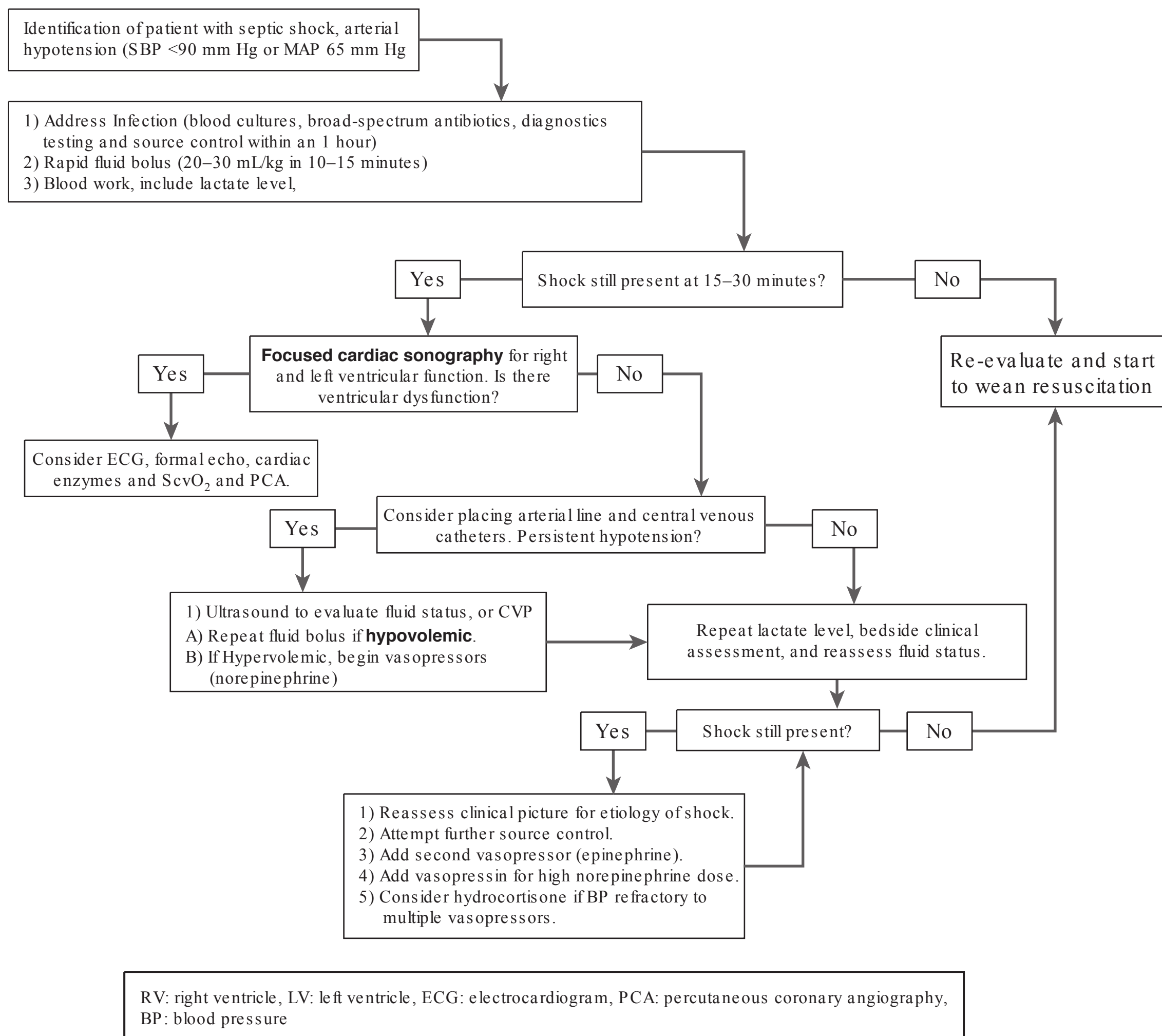


FIGURE 45-1 An algorithmic approach to septic shock. (Data from Seymour CW, Rosengart MR: Septic Shock: Advances in Diagnosis and Treatment. *JAMA*. 2015 Aug 18;314(7):708–717.)

ICU are both being examined closely, and further refinement of guideline-based treatment is evolving rapidly. Regardless, early recognition and antibiotic administration, volume resuscitation, vasopressors, and other therapies for physiologic support are essential for the good outcomes of these challenging patients.

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Hospital-Acquired, Health Care-Associated and Ventilator-Associated Pneumonia

Alexandra Franco • Carlos H. Moreno • Claudio Tuda

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INTRODUCTION

Whether in the emergency department (ED) or in the intensive care unit (ICU), pneumonia is a disease with which all treating clinicians must be familiar. Acute pneumonia is the fourth leading cause of death among patients of all age groups worldwide and the leading cause of mortality in low-income countries according to the World Health Organization (WHO).¹ The main challenge in the management of this illness is the large number of microbial agents that can cause the disease, in addition to the difficulty of making an etiologic diagnosis before starting treatment. Therefore, antibiotic therapy must be started empirically by clinicians, which may lead to excessive antibiotic coverage, which entails a considerable risk of antibiotic resistance among the common pathogens involved. In order to accurately recognize and appropriately manage pneumonia, healthcare providers must understand the different definitions, microbiology, pathogenesis, and varying treatment guidelines available.

DEFINITIONS

Pneumonia is classified depending on where and when the patient becomes infected. The most updated guidelines from the joint committee between the American Thoracic Society (ATS) and the Infectious Diseases Society of America (IDSA) in 2005² and 2007,³ respectively, focus on evidence-based recommendations for four different categories of pneumonia: community-acquired pneumonia (CAP), hospital-acquired pneumonia (HAP), healthcare-associated pneumonia (HCAP),

and ventilator-associated pneumonia (VAP). CAP refers to the lower respiratory infection obtained from normal social contact in the community and will not be discussed in this chapter. Moreover, the category previously known as nosocomial pneumonia now comprises three different clinical settings of infection in patients exposed to different healthcare settings and invasive procedures. HAP is defined as pneumonia that occurs 48 hours or more after admission to the hospital and that was not incubating at the time of that admission. HCAP refers to pneumonia in patients who were acutely hospitalized for two or more days within 90 days of the actual infection; resided in nursing homes or long-term care facilities; received recent intravenous antibiotic treatment, chemotherapy or wound care within the past 30 days of the actual infection; or underwent hemodialysis. Last, VAP includes any patient who develops pneumonia 48 to 72 hours after endotracheal intubation.

As proposed by the 2005 ATS/IDSA guidelines, the main microbiologic difference between CAP and pneumonias acquired from healthcare settings is the risk for infection with multidrug-resistant (MDR) bacteria that impairs the response to common empiric antibiotic treatment and affects the outcome. Once a patient has been diagnosed with HAP, HCAP or VAP, clinicians must immediately assess the patient's risk factors for MDR organisms, which will guide the subsequent antibiotic selection (Table 46-1).

EPIDEMIOLOGY

In 2011, 4% of inpatients in the United States had at least one healthcare-associated infection, yielding an estimate of



TABLE 46-1: Risk Factors for Multidrug-Resistant Pathogens Causing Hospital-Acquired Pneumonia, Healthcare-Associated Pneumonia, and Ventilator-Associated Pneumonia

- Antibiotic therapy within the preceding 90 days
- Current hospitalization of more than 5 days
- High-frequency antibiotic resistance in community or specific ICU
- Immunosuppressive disease or therapy
- Presence of risk factors for HCAP
 - Hospitalization for more than 2 days in the preceding 90 days
 - Residence in a nursing home or extended-care facility
 - Home infusion therapy (including antibiotics)
 - Chronic dialysis within 30 days
 - Home wound care
 - Family member with multidrug-resistant pathogen

721,800 new infections in one year. HCAP and surgical-site infections were the most common healthcare-associated infections, accounting for almost 44% of the episodes. Mechanical ventilation was associated with 39.1% of HCAP events. The three most common pathogens proven to be involved in cases of HCAP were *Staphylococcus aureus*, *Klebsiella pneumoniae* or *oxytoca*, and *Pseudomonas aeruginosa*. According to different surveys around the country and as reported by the National Healthcare Safety Network (NHSN), on any given day, approximately 1 of every 25 patients admitted to the hospital will develop at least one healthcare-associated infection, most commonly HCAP.⁶

A per-case cost meta-analysis published in the *Journal of the American Medical Association* in 2013 revealed that one case of VAP will cost around \$40,144, being the second most costly healthcare-associated infection after central line-associated events. The total annual cost for the 5 major causes of healthcare-associated infections was approximately \$9.8 billion, with HCAP contributing to 31.6% of this expenditure.⁷ A different study in 2010 among Medicare beneficiaries showed an incidence of pneumonia cases, of any classification, of 47.4 cases per 1,000 patients. Of these cases, almost 50% were treated as inpatients and 30-day mortality was twice as high in patients with HCAP when compared to patients diagnosed with CAP (13.4% vs. 6.4%). The total annual cost of hospital-treated pneumonia was calculated to be more than \$7 billion among Medicare beneficiaries.¹¹

Compared with the estimated 10% mortality with CAP, one review of over 4,500 hospitalized patients demonstrated comparable mortalities of 19.8% with HCAP and 18.8% with HAP.⁸

Increased mortality rates in patients with HCAP are multifactorial. Clinicians previously correlated fatalities with the high incidence of MDR pathogens seen. However, many studies have consistently identified HCAP to include elderly patients with numerous comorbidities in addition to the several risk factors for infections with MDR organisms, yielding a significantly higher length of hospital stay, mortality rate, and much worse outcomes when compared with CAP

patients.⁹ Nonetheless, even in settings of low antibiotic resistance, studies have shown that patients with HCAP had worse prognostic scores on admission and higher mortality rates when compared to patients admitted with CAP. This fact suggests that infection with MDR pathogens is not as compelling as it was thought to be and is only one of the many variables that predispose patients with HCAP to worse outcomes.¹⁰ Recent observational cohort studies even suggest that not all patients with HCAP require empirical treatment for *Staphylococcus aureus* and *Pseudomonas aeruginosa*, as originally suggested, proposing that there is not enough evidence to support broad-spectrum empirical antibiotic management.^{10,12} ATS/IDSA guidelines recommendations from 2005 in favor of categorization of different pneumonia types and early broad-spectrum antibiotic therapy for HCAP are now controversial²⁰ and updates are under development.

Occurring in 10% to 27% of all intubated patients,^{13–15} VAP accounts for approximately 40% of the HAP cases and estimates of incidence range from 4 to 7 cases per 1,000 patients on mechanical ventilation.⁶ In 2008, the Society for Healthcare Epidemiology of America (SHEA) and the IDSA published strategies to prevent VAP in acute care hospitals, which were recently updated in 2014, reporting that mortality related to VAP alone is difficult to determine due to the numerous other complications that often occur simultaneously with VAP: acute respiratory distress syndrome (ARDS), pneumothorax, atelectasis, mucus plugging, lung collapse, pulmonary edema, pulmonary embolism, and other fatal problems, now known as ventilator-associated events (VAEs). Despite variations in different studies, the attributable overall mortality of VAP is estimated to be 10%.^{14,15} By 2002, VAP was increasing time on mechanical ventilation, length of hospital and ICU stay, and the cost of hospitalization per patient by \$40,000.¹⁶

PATHOGENESIS

The lungs are constantly exposed to a mixture of gases, foreign material, and microbes inhaled from the outer environment. Nonetheless, the lower respiratory tract remains sterile due to the host defense mechanisms that include anatomic and mechanical barriers, an innate phagocytic activity, and adaptive cell-mediated and humoral immunity. When functioning normally, the host defense mechanisms are extraordinarily efficient in preserving the sterile milieu of the lungs. Community-acquired and pneumonia obtained from healthcare settings occur as a consequence of either an abnormal host defense, exposure to an extremely virulent organism, or a significant inoculum. Microorganisms may reach the lower airways most commonly through micro-aspiration of colonized nasal or oropharyngeal secretions, but also from inhalation of aerosolized pathogens, direct inoculation from nearby foci or microbes coming from distant extrapulmonary sources through the bloodstream.

Several other factors are associated with the malfunctioning of the host defense and promote bacterial overgrowth, contributing to the development of pneumonia. Common

examples are immunosuppression; swallowing difficulties or alterations in the patient's mental status that debilitate the epiglottic closure and favor aspiration (e.g., strokes, neuromuscular disorders, alcohol abuse, sleep); cigarette smoking, which acts as an insult to anatomic and mechanical barriers; poor cough reflex with subsequent pooling of bacteria; previous antibiotic exposure, which eliminates indigenous gastrointestinal bacteria and stimulates replication of resistant strains; and acid-suppressive medications that increase gastric pH, promote bacterial overgrowth, and induce regurgitation and micro-aspiration.⁴

Patients admitted to the hospital may get rapidly colonized with microorganisms from the hospital environment. Different studies have shown how colonization may happen quickly, and in the critically ill patient may take as little as 48 hours.^{17–19} Colonization results from exposure to, and direct contact with, contaminated devices, water reservoirs, healthcare providers' hands, and medical equipment. In addition, the pathogenetic changes in the host related to medications, illness, or malnutrition may also increase susceptibility.

The pathogenesis of VAP shares these same pathologic characteristics but involves the presence of an endotracheal tube (ETT), which directly bypasses the upper airways' protective mechanisms and maintains a humid media that benefits bacterial replication and formation of a gelatinous substance called "biofilm." Biofilm prevents antibiotic penetration and allows a steady bacterial replication rate, which could serve as a source for recurrent pneumonia. Although intubation is the single most important risk factor for the development of VAP,⁵ bacteria can also access the lungs from other colonized ventilator apparatus or nasal tubes (e.g., humidifiers, filters, suction catheters, nasotracheal tubes, nasogastric tubes), resulting in a harmful inoculum of bacteria in the lungs.

MICROBIOLOGY

Because of the relative ease of obtaining culture specimens from mechanically ventilated patients, more microbiologic data are available for VAP compared with other forms of pneumonia. However, due to shared risk factors for MDR organisms, the causative bacteria for HAP, HCAP, and VAP are considered to be quite similar.²

Individuals developing symptoms within the first 48 to 72 hours of hospital admission are considered at risk of HAP, but could be showing signs of infection from the community. As per the 2005 ATS/IDSA guidelines, despite the possibility of community-acquired infection, these patients are entitled to broad-spectrum antibiotic therapy from the beginning. This concept is now controversial, however.^{10,12,20}

HAP, HCAP, and VAP have a wide variety of microbiologic etiologies, and could even present as polymicrobial infections. *Staphylococcus aureus*, including methicillin-sensitive and methicillin-resistant strains, is the most common pathogen involved, with an incidence ranging from 17% to 47% of all HCAP and VAP cases. Up to 50% of the cases of *S. aureus* are due to methicillin-resistant *S. aureus* (MRSA).^{8,23} The second and third most common etiologies are the aerobic

gram-negative bacilli *Pseudomonas aeruginosa* and the *Klebsiella* species, respectively.^{2,6,20–22} A fairly large study done in 2007 still postulates *Streptococcus pneumoniae* as the single most common bacterial etiology in both CAP and HCAP, with the difference that more resistant strains of pneumococci were seen in HCAP cases.²⁴ One multistate prevalence survey published in the *New England Journal of Medicine* in 2013 reported few cases of HAP, HCAP, and VAP associated with *Stenotrophomonas maltophilia* (5.5%), *Acinetobacter baumannii* (3.6%), *Enterobacter* species (2.7%), *Citrobacter* species (1.8%), *Serratia* species (1.8%) and *Fusobacterium* species (less than 0.9%).⁶

Every community hospital and ICU has its own bacterial resistance patterns that continue to evolve along with antibiotic prescribing practices; thus, the initial antibiotic regimen must be suited to current local susceptibilities.^{2,25}

DIAGNOSIS

Three main objectives exist when evaluating a patient for the possibility of HAP or HCAP: confirming its presence, grading its severity, and identifying a microbiologic etiology.²⁷

The 2005 ATS/IDSA guidelines did not propose clinical diagnostic criteria for suspicion of HAP and/or HCAP. According to this consensus, the diagnosis of HAP or HCAP should be suspected when a patient has a radiographic infiltrate that is new or progressively worsening, along with clinical findings suggestive of respiratory infection that include fever, purulent sputum, leukocytosis, and decline in oxygenation.² Other literature reviews propose a clinical diagnosis of HAP or HCAP with a radiographic finding that presents with at least 2 of 3 clinical criteria^{2,26} (Table 46-2). If clinical findings are present in the absence of radiographic findings, tracheobronchitis is likely a more suitable diagnosis.²

In order to grade pneumonia severity, many scoring systems have been proposed. A complex 12-point scale called the Clinical Pulmonary Infection Score (CPIS) was developed in the early 1990s,²⁸ but further studies showed a sensitivity of only 60% to 77% and a specificity of 42% to 75%, making it a very inaccurate scoring tool.^{29,30} A clinical prediction rule initially developed for CAP, known as the CURB-65 or CURB criteria, has been well established and used by clinicians when suspecting CAP. Recently, this score has been applied to the setting of HAP and HCAP as well. This score predicts the need for admission to an acute care



TABLE 46-2: Clinical Diagnosis of HAP and HCAP

- Presence of new or progressive radiographic infiltrate plus
- At least two of the following three:
 - Fever > 38°C
 - Leukocytosis > 12,000 white blood cells/μL or leukopenia < 4,000 white blood cells/μL
 - Purulent tracheobronchial secretions

facility for inpatient treatment of pneumonia, and predicts mortality. The score is an acronym for each of the variables measured, which gives 1 point for each variable present, for a maximum score of 5 points (Table 46-3). Another widely

used severity scoring system is the Pneumonia Severity Index (PSI), which is calculated using an online, automated calculator (Table 46-3). The latter was also designed for CAP but has gained use in HAP and HCAP patients. The data on the



TABLE 46-3 Estimates Mortality of Community-Acquired Pneumonia to Help Determine Inpatient vs. Outpatient

CURB-65	PSI	
<ul style="list-style-type: none"> • Confusion: New onset and defined as an AMTS of 8 or less)^a • Uremia: blood urea nitrogen > 19 mg/dL or 7 mmol/L • Respiratory rate > 30 respirations per minute • Blood Pressure: Systolic < 90 mm Hg or diastolic < 60 mm Hg • Age 65 or older 	<p>STEP 1: Stratify risk class I vs Risk class II-V</p> <p>Presence of</p> <ul style="list-style-type: none"> • Age over 50 years • Altered mental status • Heart rate > 125 beats per minute • Respiratory rate > 30 respirations per minute • Systolic blood pressure < 90 mm Hg • Temperature < 35°C or > 40°C <p>History of</p> <ul style="list-style-type: none"> • Neoplastic disease • Congestive heart failure • Cerebrovascular disease • Renal disease • Hepatic disease <p>If all answers are “NO,” classify as risk class I. If any “YES,” proceed to step 2.</p> <p>STEP 2. Stratify risk class II vs. risk class III vs. risk class IV vs. risk class V</p> <p>Demographics</p> <ul style="list-style-type: none"> • If male + Age in years • If female (+ Age in years) – 10 • Nursing home resident + 10 <p>Comorbidities</p> <ul style="list-style-type: none"> • Neoplastic disease + 30 • Hepatic disease + 20 • Congestive heart failure + 10 • Cerebrovascular disease + 10 • Renal disease + 10 <p>Physical Exam Findings</p> <ul style="list-style-type: none"> • Altered mental status + 20 • Heart rate > 125 beats per minute + 10 • Respiratory rate > 30 respirations per minute + 20 • Systolic blood pressure < 90 mm Hg + 20 • Temperature < 35°C or greater than 40°C + 15 <p>Lab and Radiographic Findings</p> <ul style="list-style-type: none"> • Arterial pH < 7.35 + 30 • Blood urea nitrogen > 9 mmol/L or 30 mg/dL + 20 • Serum sodium < 130 mmol/L + 20 • Glucose > 250 mg/dL + 10 • Hematocrit < 30% + 10 • Partial pressure of arterial O₂ < 60 mm Hg + 10 • Presence of pleural effusion + 10 <p>Σ < 70: Risk Class II, 0.6–0.9% mortality. Outpatient treatment</p> <p>Σ 71–90: Risk Class III, 0.9–2.8% mortality. Outpatient or inpatient base on clinical judgment.</p> <p>Σ 91–130: Risk Class IV, 8.2–9.3% mortality. Hospitalization recommended based on risk.</p> <p>Σ > 130: Risk Class V, 27.0–29.2% mortality. Hospitalization recommended</p>	<p>YES/NO answer for each item</p> <p>Points assigned^b</p>

^aAMTS: Abbreviated mental test score³²

^bThe automated calculator will add the points and give a final score by the end of the questionnaire.

use of PSI and CURB-65 in HCAP is limited. A retrospective analysis published by the *Clinical Infectious Diseases* journal in 2013 demonstrated that the performances of PSI and CURB-65 for predicting 30-day mortality in patients with HCAP were comparable to those in patients with CAP with lower discriminatory powers.³¹

Microbiologic diagnostic methods attempt to regain a suitable degree of specificity via the acquisition and culture of causative pathogens. Despite numerous studies, the most accurate method of obtaining a bacterial specimen that is representative of the lower respiratory tract is still unclear. Some studies advocate that culturing specimens from the lower respiratory tract through more invasive procedures—such as bronchoscopy with bronchoalveolar lavage (BAL) or bronchial brushing, also known as protected specimen brush (PSB)—enhances the specificity of the samples.

Major global recommendations for diagnosis of HAP or HCAP include obtaining a complete and comprehensive medical history, which helps clinicians exclude other sources of infection in addition to the following items. All patients should have a chest radiograph, preferably with posteroanterior and lateral views. Arterial oxygenation should always be measured. Arterial blood gases should be obtained only with concerns of acid–base disturbances. Blood culture specimens ideally should be obtained before any antibiotic treatment is started. Sputum specimens of the lower respiratory tract should be obtained in all patients with suspicion of HAP or HCAP, ideally by endotracheal aspirate, BAL, or PSB samples. Upon suspicion of complications with pleural effusions or empyema, a diagnostic thoracentesis should be performed. In the presence of ARDS, with which it is difficult to assess radiographic findings, at least two of the three clinical criteria must be present in order to suspect HAP or HCAP (Table 46-2).²

Quantitative cultures use a predefined logarithmic threshold of bacterial growth to attempt to differentiate colonization from infection. This diagnostic threshold varies according to the sampling method used: endotracheal aspirate 10^6 colony-forming units (CFU)/mL, BAL 10^4 CFU/mL, and PSB 10^3 CFU/mL. Nonetheless, these thresholds have been considered flawed by many experts due to inconsistencies yielded by individual patient characteristics, type of microorganism involved, history of prior exposure to antibiotics, volume of the specimen, collection techniques, anatomic location of the specimen obtained, and methods of bacterial analysis.³³

TREATMENT

According to the 2005 ATS/IDSA guidelines, once the clinical and radiographic diagnosis has been made, the clinician must make the decision to initiate empirical antibiotic treatment depending on the different risk factors for MDR organisms.² The overall basic approach to treatment of HAP is shown in Figure 46-1.

Notwithstanding the prior guidelines, many studies and academic clinicians have criticized the categorization and recommendation of early broad-spectrum antibiotic treatment

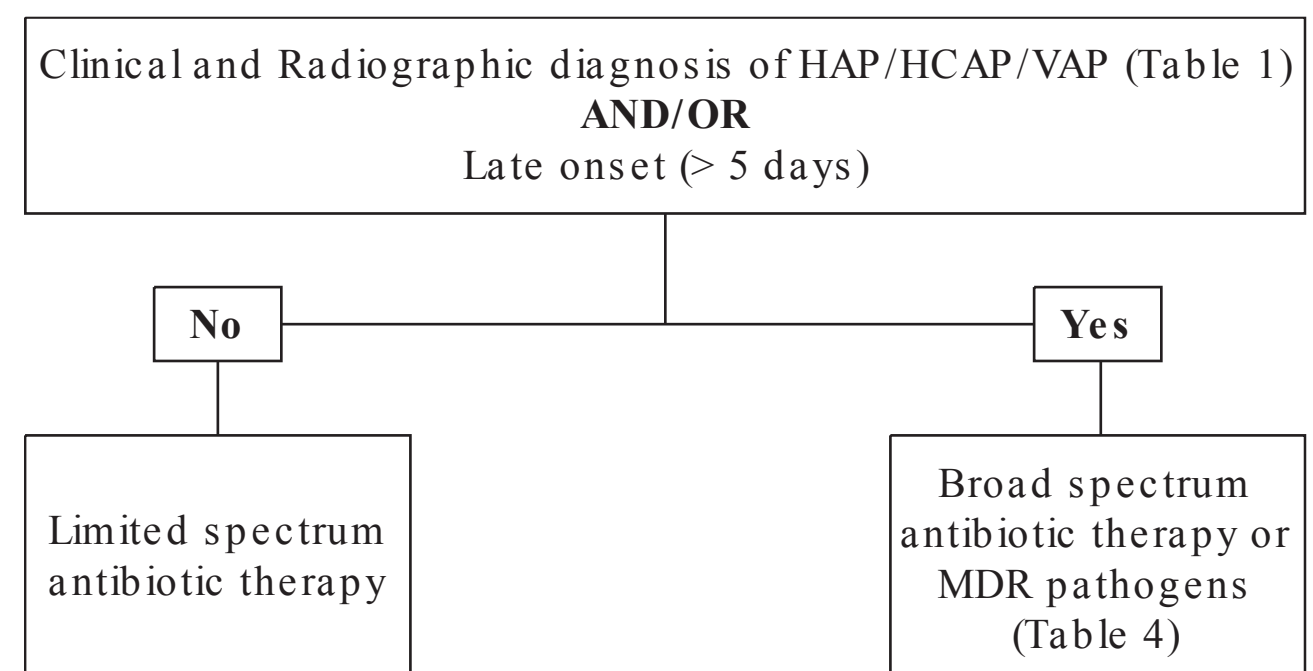


FIGURE 46-1 2005 ATS/IDSA guidelines for the management of adults with HAP, VAP, and HCAP.² Algorithm for initiating empirical antibiotic therapy.

based on risk factors for MDR organisms. Several studies suggest that the increased mortality in patients with HCAP is primarily related to underlying patient-related factors and comorbidities rather than associated with MDR pathogens.⁴⁰

A detailed review published in *The Lancet Infectious Diseases* in 2011³⁴ described that the single most important risk factor for MDR pathogen-related infections is the previous exposure to antibiotics. This illustrates the vicious cycle created by the 2005 guidelines and a dangerous overuse of antibiotics, and questions the real risk versus the benefit of early broad-spectrum antibiotic management in suspicion of HAP and HCAP (Figure 46-2).

Recently, it has been estimated that approximately 30% to 70% of the patients who develop progressive radiographic

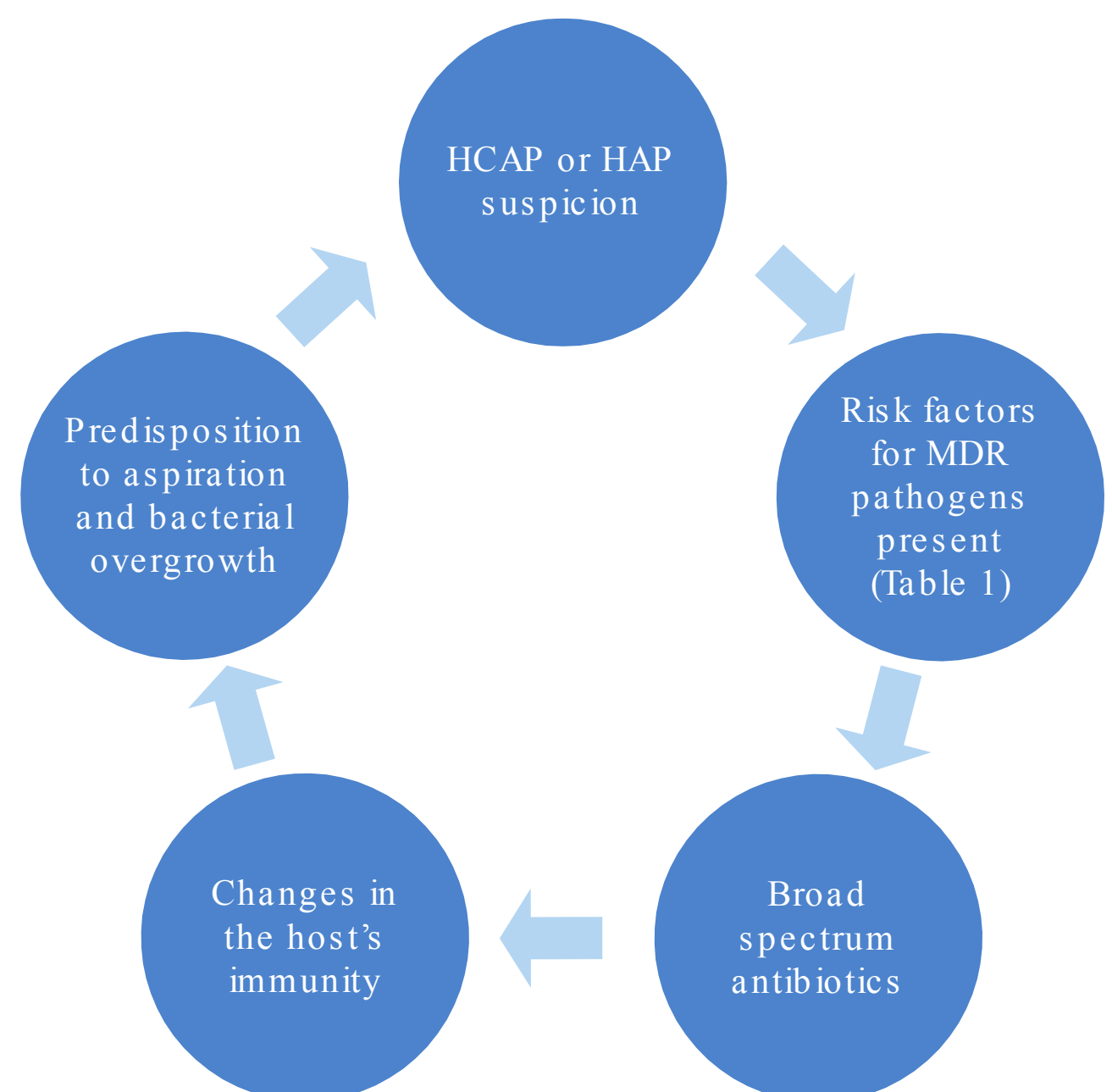


FIGURE 46-2 The vicious cycle between broad-spectrum antibiotics and risk factors for MDR organisms-related infections.³⁴

findings and who receive broad-spectrum antibiotic therapy are not infected with pneumonia.^{35,36} Contrast this with the fact that the US Centers for Medicare and Medicaid Services (CMS) has penalized emergency medicine physicians if antibiotics for CAP were not given within the first 6 hours of presentation to an ED. This has created an overprescription of antibiotics among emergency medicine physicians that places patients at high risk of further infections with MDR organisms and new exposure to broad-spectrum antibiotics.³⁷

After all the controversy, the key is to individualize every patient and treat each case accordingly.

For severe cases with low risk for MDR pathogens, monotherapy has been proposed with second- or third-generation cephalosporins, β -lactams plus a β -lactamase inhibitor, monobactams, or fluoroquinolones. Monotherapy is not recommended for patients known to have an infection with an MDR pathogen or in cases with high suspicion for MDR infection. Combination therapies suggested are antipseudomonal cephalosporins, carbapenems, or anti-pseudomonal β -lactam/ β -lactamase inhibitor *plus* fluoroquinolones or aminoglycosides *plus* coverage for MRSA if it is a consideration based on presentation or regional infection patterns.

Vancomycin was the only antibiotic effective against MRSA for many years. New antibiotic options, however, have demonstrated efficacy when compared with vancomycin. In the VAP setting, linezolid showed improved survival and faster cure rates when compared to vancomycin.³⁸ For HAP patients, telavancin was demonstrated to be noninferior to vancomycin on the basis of clinical response.³⁹ Telavancin was approved by the Food and Drug Administration (FDA) in 2013 for the use of MRSA-related HAP, HCAP, and VAP. Off-label use of medications effective against MRSA but that have not been approved by the FDA yet include ceftaroline and tigecycline.

Currently, *Pseudomonas aeruginosa* coverage with monotherapy versus combination therapy is controversial. Initial recommendations suggest a minimum of 5 days of combination therapy with a β -lactam *plus* an aminoglycoside with proper de-escalation afterwards.

Duration of therapy should be determined by the clinical response. The mainstay of the treatment regimen is to find the etiologic agent. If the patient improves within 48 to 72 hours of treatment and a pathogen has been isolated, antibiotic coverage should be de-escalated. More than 7 days of pathogen-directed treatment with common pathogens have shown no benefit when compared to longer courses.^{42,43} Overall duration of therapy recommendations with *Pseudomonas aeruginosa* are 14 days and 21 days with MRSA.

In cases when the patient is showing clinical improvement but no pathogen is isolated, the recommendation is to narrow the spectrum, discontinue *Pseudomonas aeruginosa* and MRSA coverage, and plan to complete a 7-day course. In patients in whom no clinical improvement is evidenced, complications from pneumonia or other sources of infection must be sought.

New proposals to use procalcitonin to guide antimicrobial treatments in patients with HAP, HCAP, and VAP are

promising. Negative procalcitonin levels prompt the physicians to stop antibiotics or give short courses in order to decrease exposure to broad-spectrum therapy. Procalcitonin-based protocols have not affected outcomes in patients who received less antibiotic days. However, more research is needed to include this tool in the treatment guidelines.⁴¹

NOVEL THERAPIES

Novel antimicrobial agents are under development for the treatment of HAP and VAP. Ceftobiprole is a broad-spectrum cephalosporin with activity against gram-negative and gram-positive bacteria (including MRSA and resistant strains of pneumococci). It has not been approved in the United States, but its use in European countries has shown promising results in patients with HAP and CAP, but not VAP.^{44,47} Avibactam—a non- β -lactam, broad-spectrum β -lactamase inhibitor added to the antipseudomonal third-generation cephalosporin, ceftazidime—is currently in phase 3 trials for HCAP, HAP, and VAP.^{45,47} Monoclonal antibodies designed to bind *Pseudomonas aeruginosa* epitopes are also in testing and are hypothesized to reduce the virulence factors associated with this organism.^{46,47}

PREVENTION

Preventing HAP and HCAP hinges on properly addressing its underlying pathogenesis, while simultaneously minimizing intubation and time on mechanical ventilation in order to prevent VAP. Strategies may include utilizing the least invasive method suitable for respiratory support, minimizing the time spent on mechanical ventilation, minimizing sedation, avoiding unnecessary medications (antibiotics, proton pump inhibitors), frequent aspiration of excessive secretions to avoid micro-aspiration and pooling of oral bacteria, enhancing immunity with early nutrition, and encouraging healthcare providers' compliance with good hand hygiene and preventive measures.

If intubation cannot be avoided, clinicians must attempt aggressive ventilator weaning as soon as possible, as well as early tracheostomy planning if extubation is unsuccessful. Simple measures such as maintaining patients in the semi-recumbent position could make a significant difference in outcomes.

In 2009, a trial of almost 6,000 ICU patients randomized to receive oral bacterial decontamination with topical antibiotics demonstrated a significant decrease in the 28-day morbidity and mortality. Clinicians have been using oral decontamination routinely ever since as part of a so-called “ventilator bundle.”⁴⁸ More recent studies of chlorhexidine given in the preintubation period in addition to daily topical regimens, however, showed no significant improvement in outcomes.⁴⁹

To prevent leakage of colonized subglottic secretions around the ETT, endotracheal cuff pressures should remain between 20 and 30 cm H₂O.^{50,51} Also, silver-coated ETTs inhibit bacterial colonization and are preferred over uncoated

ETTs.⁵² There is a lack of evidence for each one of these preventive measures alone, and individually these strategies probably have very modest effects. However, when implemented together as part of a “ventilator bundle,” dramatic positive effects have been shown.⁵³

The proactive application of preventive measures for HAP, HCAP, and VAP can reduce morbidity and mortality rates and, at the same time, will reduce length of hospital and ICU stay with significant reductions in healthcare expenditures.

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Infectious Endocarditis

Joseph R. Shiber

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INTRODUCTION

Endocarditis, inflammation of the endocardial surface of the heart, can have numerous etiologies, including mechanical irritation, neoplastic, autoimmune, or infectious diseases.¹⁻⁴ This chapter will focus on the infectious causes, which are typically bacteria, mycobacteria, and fungi. Although the cardiac valves are most commonly involved, the mural endocardium, septal defects, chordae tendineae, and even intracardiac medical equipment (pacemaker/defibrillator leads or septal occluder devices) can also be sites of infection.¹⁻⁶ Infectious endocarditis (IE) has an incidence of 3.6/100,000 per year and accounts for 1/1,000 hospital admissions in the United States. There is a 2:1 male to female ratio, with current overall inpatient mortality between 11% and 26%, although this figure may be drastically different for the various subsets of IE patients.^{1,3,7} The incidence and mortality of IE has not changed over the last 30 years.⁸

CLASSIFICATIONS

The first published description of valvular cardiac lesions due to IE was over 300 years ago by Lazarus Riverius. About 200 years ago, Jean Baptiste Boulaud defined the anatomy of the endocardium; 150 years ago, the association of preexisting rheumatic valvular damage and bicuspid aortic valves with IE

was noted by Sir James Paget.^{9,10} In 1905, when blood cultures came into clinical practice, the antemortem diagnostic rate for IE was approximately 50%.¹⁰ IE has had numerous classification schemes over the last century, starting with Sir William Osler, who divided IE into “simple” and “malignant” categories based on the length of time from symptom onset to death along with the associated complications. These categories evolved into the following IE classifications in the preantibiotic era: (1) acute (onset of symptoms to death < 6 weeks, caused by a highly virulent organism capable of infecting a normal heart); (2) subacute (onset of symptoms to death 6 weeks to 3 months, caused by a less virulent organism that infects hearts with preexisting endocardial damage); (3) chronic (> 3 months from symptom onset to death, caused by an indolent microbe capable of infecting only abnormal hearts or immunosuppressed patients).^{10,11} Current classifications include diagnostic status (definite or probable), anatomic site (right- or left-sided cardiac valves), valve type (native or prosthetic), microbe (bacterial or fungal species), and patient population (intravenous [IV] drug abusers [IVDA], elderly, nosocomial infection). Prosthetic valve IE is further divided into early (< 2 months after surgery), intermediate (2 months to 1 year), and late (> 1 year after surgery) cases; the early cases are typically nosocomial, while the intermediate and late cases are community acquired.¹¹⁻¹³ Another classification that reflects the early description by Osler is simple (infection

limited to valve cusps and leaflets) or advanced (deep-tissue infection, including perivalvular structures, cardiac abscess or pseudoaneurysm formation, and systemic infectious emboli). These various categories of IE differ in incidence, presentation, microbial etiology, and outcome.^{1,3,11,14}

ETIOLOGY

The disease process of IE and vegetation formation requires multiple steps (see Figure 47-1) starting with endothelial

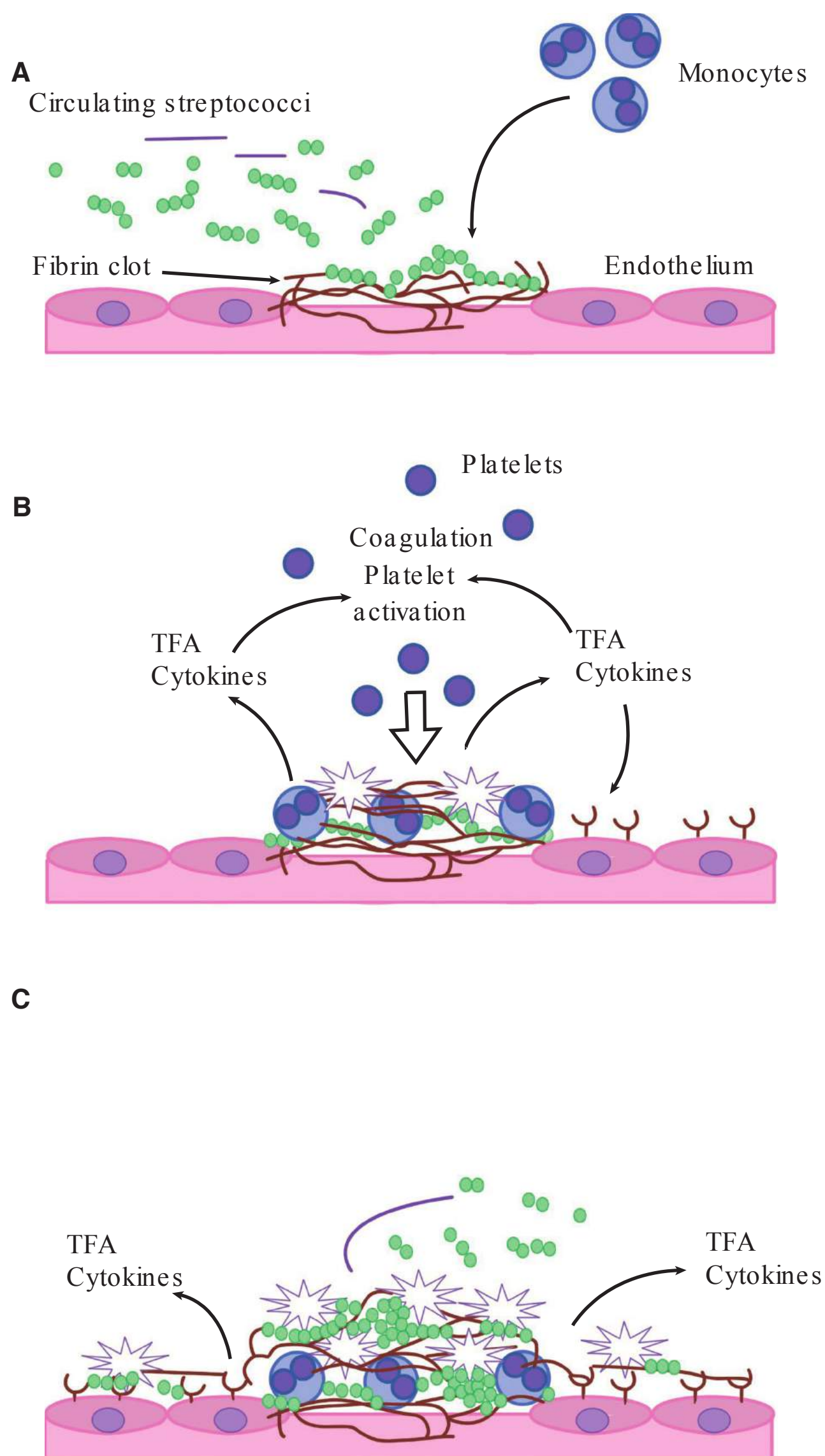


FIGURE 47-1 Pathogenesis of bacterial valve colonization. Viridans group streptococci adhere to fibrin–platelet clots that form at the site of damaged cardiac endothelium (A). The fibrin-adherent streptococci activate monocytes to produce tissue-factor activity (TFA) and cytokines (B). These mediators activate the coagulation pathway, resulting in further recruitment of platelets and growth of the vegetation (C). (Reproduced with permission from McPhee SJ, Ganong WF: *Pathophysiology of Disease: An Introduction to Clinical Medicine*, 5th edition. New York: McGraw-Hill Inc; 2006.)

damage from high-velocity jets of blood due to congenital or acquired cardiac abnormalities, or mechanical damage from intracardiac devices or blood-borne debris.^{1,11} Platelets and fibrin then form a sterile thrombus at the site of endothelial damage; certain disease states, such as malignancy, uremia, and autoimmune diseases, can form sterile cardiac vegetations without overt endothelial damage. The initially sterile site is seeded by transient bacteremia and then matures with additional fibrin deposition and bacterial proliferation. The vegetation has no vasculature; thus, it is relatively protected from activated phagocytes or antibiotic penetration.^{11,12}

In developing countries, rheumatic heart disease is still the main risk for IE; as treatment of streptococcal pharyngitis improved in the United States and Europe, there has been less cardiac sequelae. Thus, in these areas, congenital (bicuspid aortic valve, hypertrophic obstructive cardiomyopathy, mitral valve prolapse with regurgitation) and degenerative cardiac diseases (aortic valve calcification) are the leading risk factors for IE. Other recognized risks include diabetes mellitus, hemodialysis, immunosuppression, and previous IE. Approximately 50% of cases have no known prior valve abnormality but likely had microscopic valvular lesions that were vulnerable to highly virulent organisms such as *Staphylococcus aureus* or *Streptococcus pneumoniae*.^{2,3,7}

MICROBIOLOGY

While streptococcal species are still the leading infectious agents for IE worldwide, their incidence has been declining with better oral hygiene and dental care plus appropriate antibiotic prophylaxis. On the other hand, *S. aureus* IE has been increasing in incidence and is the leading cause in intensive care unit (ICU) cases and in IVDA. It is also the leading cause of all IE cases in Western countries now. Of all infections due to *S. aureus*, IE has the highest mortality rate. The IE cases due to *S. aureus* in the United States are 40% due to methicillin-resistant *Staphylococcus aureus* (MRSA) and 60% due to methicillin-sensitive *Staphylococcus aureus* (MSSA).¹⁵ In non-IVDA native valve endocarditis (NVE), streptococcal species (*S. viridans*, *S. mutans*, *S. mitis*, *S. sanguis*) typically from the mouth and nasopharynx account for 17% to 36% of cases; *Streptococcus bovis* accounts for 6% and is associated with gastrointestinal (GI) lesions in the elderly. *S. aureus* accounts for up to 30% of the cases in this category, with the skin as the major source. In half of the cases, however, there is no obvious portal of entry, so that nasal carriage is also a source. *Enterococcus* species cause 8% to 11% of the NVE in non-IVDA patients, who are mostly older with GI/genitourinary (GU) lesions or recent procedures. The *Haemophilus*, *Actinobacillus*, *Cardiobacterium*, *Eikenella*, and *Kingella* (HACEK) group accounts for only 3% of cases in this population; although Gram-negative bacilli (GNB) are leading causes of sepsis, their lack of avid adherence to endothelium diminishes the risk of IE during bacteremia. *S. pneumoniae* causes a small number of cases of NVE in a subset of non-IVDA patients with diabetes mellitus, malignancy, chronic obstructive pulmonary disease (COPD), or alcoholism; the

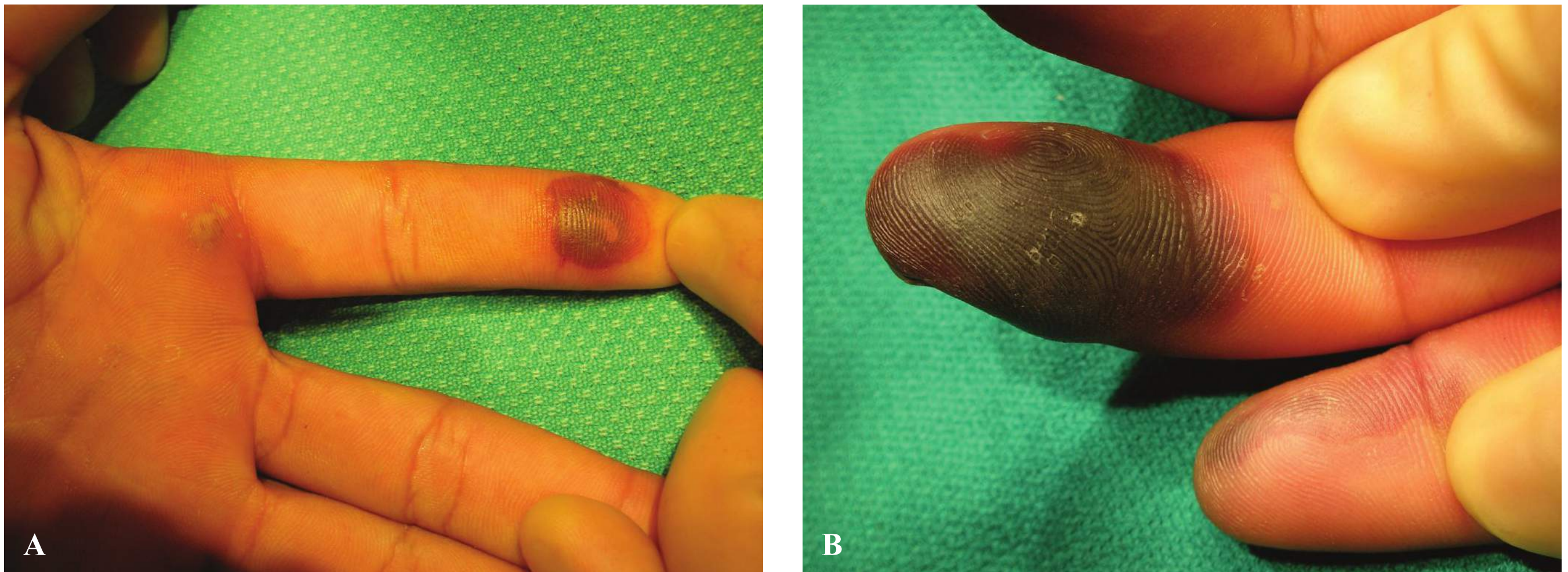


FIGURE 47-2 Photographs of a young man with *Streptococcus pyogenes* endocarditis demonstrating: **(A)** Two septic emboli of the left index finger (metacarpal head and finger tip); the large pustular lesion was aspirated by the author immediately prior to the photograph and demonstrated the organism by Gram stain. **(B)** Septic emboli with necrosis of the tips of the right middle and ring finger.

lungs are the source, and meningitis is associated in 40% to 60% of patients. Fungal or polymicrobial IE is uncommon in patients with NVE who are not IVDAs.^{1,2,7,16}

In the IVDA population, there is a 2% to 5% per year risk of IE. It is higher with cocaine than heroin due to the shorter duration of cocaine, which requires more frequent injections but not heating of the drug; this may decrease the bacterial counts with heroin “cooking.” *S. aureus* is the number one microbe in this group, with the majority being methicillin-sensitive. Fungus, predominantly *Candida* and *Aspergillus* species, accounts for about 10% of IE cases in drug abusers. *Pseudomonas aeruginosa* can also be responsible for IE when unboiled tap or toilet water is used to rinse drug paraphernalia or to dissolve drugs for injection. Polymicrobial IE is unique to this population, in which it accounts for 2% to 5% of cases. Human immunodeficiency virus (HIV) infection is an independent risk factor for IE in the IVDA and is associated with increased mortality as the CD4 cell count is decreased below 200 cells/mm³. It should be noted that IE is usually not considered a complication of acquired immune deficiency syndrome (AIDS) and is quite rare in non-IVDA patients with HIV infection. When this patient type develops IE, atypical organisms such as *Salmonella* are often responsible.^{17–19}

PRESENTATION

The typical presentation of fever and cardiac murmur with skin and conjunctival lesions may not necessarily be present; in cases of very acute IE due to aggressive organisms, the classic cutaneous and retinal immunologic findings will be absent. Although 85% of patients with IE have a murmur, they may not have a murmur at initial presentation but may develop it only during the course of their illness. Obvious signs of bacterial emboli (see Figure 47-2A and B) are indicative of IE on physical examination when present in approximately 50% of cases.^{1,5}

COMPLICATIONS

At least one complication occurs in 57% of cases, with 26% having two and 14% having three or more complications. Complications of IE are divided into the two categories—cardiac and extracardiac—with the overwhelming majority of complications occurring early in the course of illness. Cardiac complications are secondary to local destruction and emboli, and include valve cusps and leaflets, chordae tendineae, atrioventricular (AV) nodal and His–Purkinje conductive tissue, myocardium (abscess, septal or free wall perforation, aneurysm), pericardium (purulent pericarditis or hemopericardium leading to tamponade), and coronary arteries (due to emboli). Congestive heart failure (CHF) is the most common complication of IE, occurring due to valvular regurgitation; myocardial failure is not a typical feature. Extracardiac complications include systemic embolization and organ failure. *S. aureus* IE is frequently associated with embolic events.²⁰ The emboli may be sterile and cause ischemia or infarction at the target organ or they may be septic and form an abscess. Alternatively, a bland infarct may be seeded by ongoing bacteremia and lead to an abscess. The most frequent sites of embolization are the brain, spleen, kidneys, skin, liver, and mesenteric and iliac arteries. A mycotic aneurysm may result at any arterial site of emboli.^{1,11,21} Risk factors for central nervous system (CNS) emboli are infection with *S. aureus* or fungi, mitral valve vegetations, vegetations > 10 mm, and mobile vegetations by echocardiography.^{20,22}

With right-sided IE, pulmonary emboli may occur, leading to septic emboli (see Figure 47-3), empyema, and right heart dysfunction. Organ failure during the course of IE is most commonly due to hemodynamic deterioration and hypoperfusion, again from valvular CHF. The exception is acute renal failure, which may be multifactorial due to acute tubular necrosis from ischemia or drugs (aminoglycosides, vancomycin, IV contrast), glomerulonephritis, or renal infarcts from

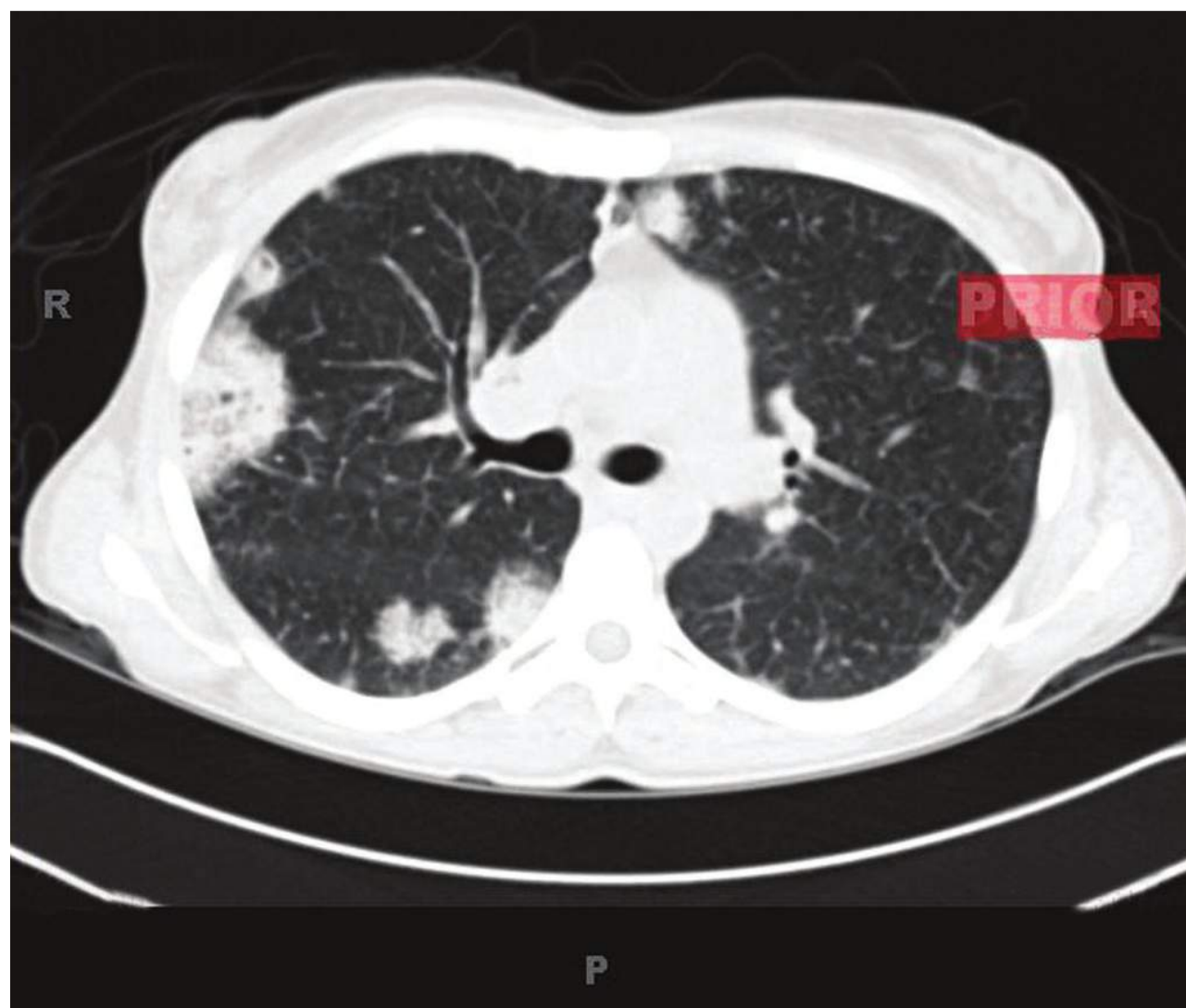


FIGURE 47-3 Chest CT of IVDA patient with tricuspid valve endocarditis due to *Staphylococcus aureus* showing multiple pulmonary emboli, some with early cavitation.

emboli (see Figure 47-4). Embolization risk is highest for large vegetations (> 1 cm diameter) particularly if involving the anterior leaflet of the mitral valve.^{2,7} Septic pulmonary emboli are typically multiple; nodular; peripheral, as 70% are just beneath the pleura; and have tendency to cavitate. CT scanning is considerably more sensitive than chest radiography in detecting these lesions.^{23,24}

With left-sided IE, CHF due to severe valvular incompetence is the most common serious complication. It occurs more frequently with aortic than mitral valve infection since the left ventricle is less tolerant of the sudden volume overload of acute regurgitation than is the left atrium. CNS complications occur in 20% to 40% of left-sided IE

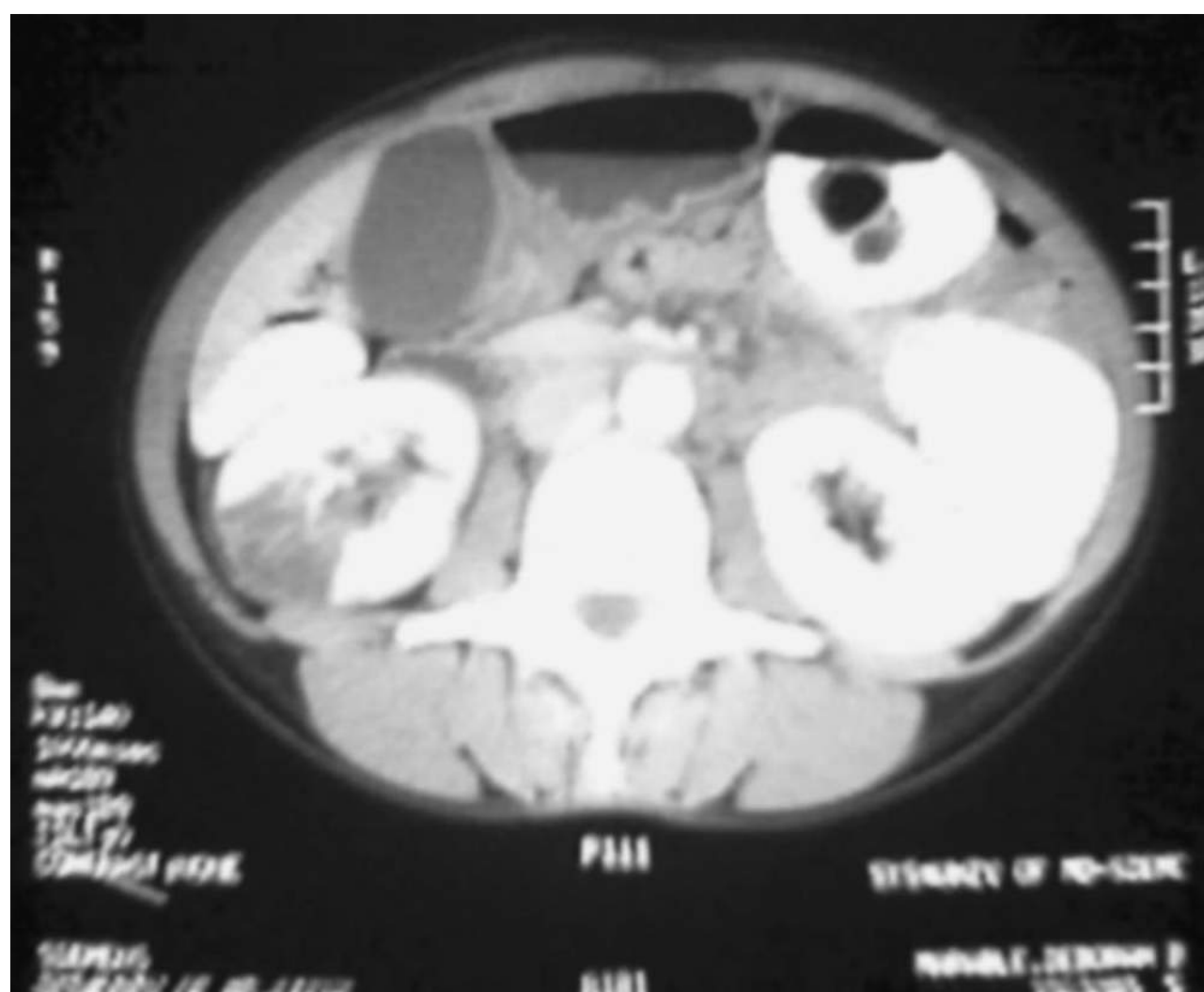


FIGURE 47-4 Abdominal CT scan with IV contrast: wedge-shaped right renal infarct in a patient with *Staphylococcus aureus* endocarditis of her mitral valve; splenic infarcts were also present.

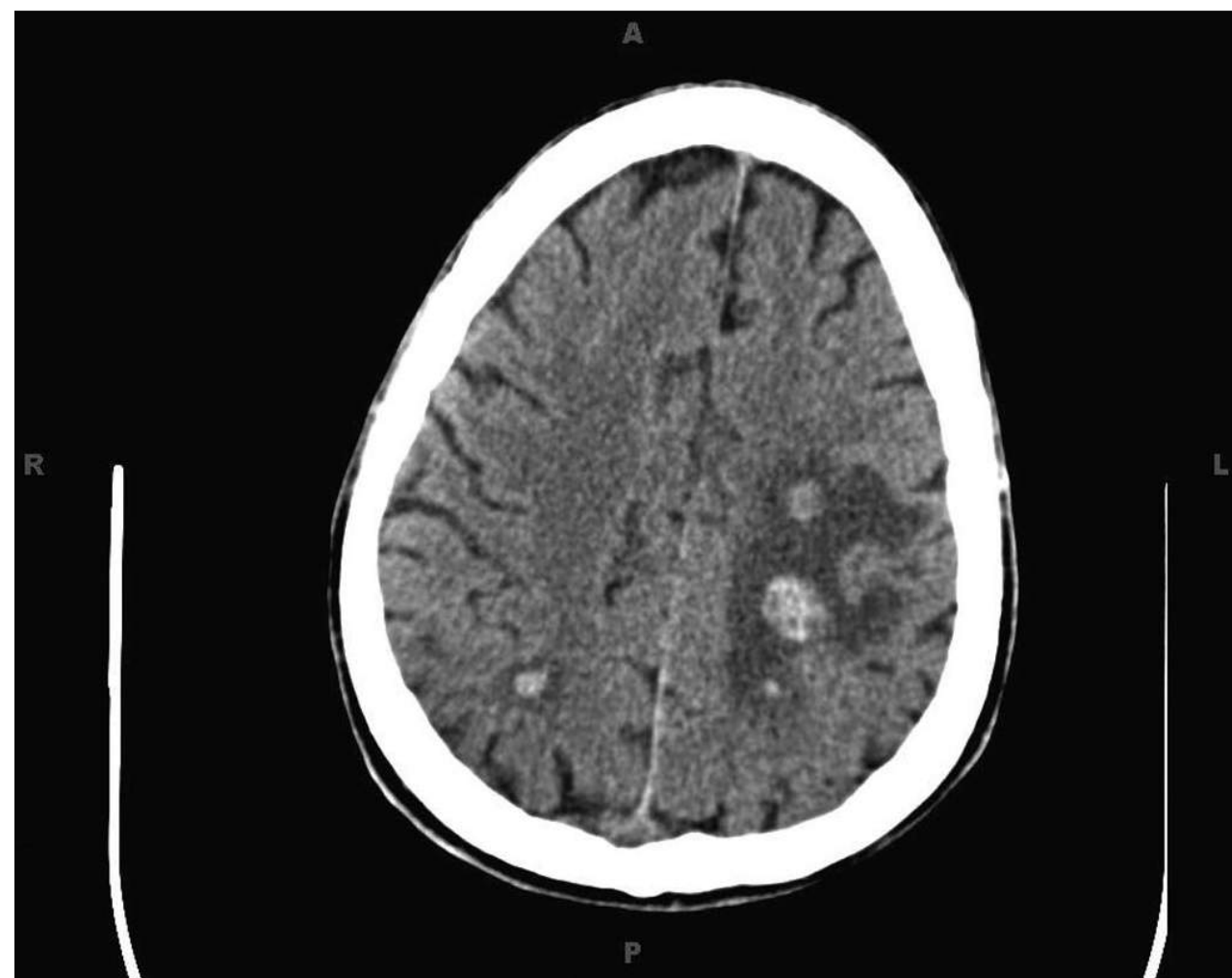


FIGURE 47-5 Multiple ischemic emboli with hemorrhagic conversion after heparin was started for an upper-extremity DVT due to a PICC line.

cases. They occur early and are the first sign of IE in 47% of patients, but the risk of further complications drops drastically after initiation of appropriate antibiotics. CNS complications are due to emboli to the cerebral arteries (the middle cerebral artery in > 90% of episodes), leading to ischemia or infarction secondary to vessel occlusion (see Figure 47-5). The resulting transient ischemic attack (TIA)/cerebrovascular accident (CVA) is the most common CNS complication of IE, representing 40% to 50% all CNS events. Brain abscess due to septic emboli accounts for only 5% of CNS events while meningitis accounts for 5% to 40%. Intracranial hemorrhage represents 10% of CNS complications of IE and can be caused by rupture of a mycotic aneurysm, septic erosion of a vessel without aneurysm (known as acute necrotizing arteritis), or hemorrhagic transformation of a recent ischemic stroke.^{1,21} Most neurologic complications from IE are present at the time of admission or within the first few days; the probability of these events decreases rapidly once appropriate antibiotics are initiated.²²

ICU ADMISSIONS

IE patients may require admission to an ICU due to septic shock, cardiogenic shock, respiratory failure, pulmonary edema from acute valve dysfunction, acute renal failure requiring renal replacement therapy, acute CNS events (stroke, intracranial hemorrhage, encephalitis), or symptomatic bradycardia/heart block requiring cardiac pacing (see Figure 47-6). Neurologic events are the most common complications of IE. Of ICU patients with IE, 55% have at least one neurologic event.²⁰ While simple IE cases can be treated by an inpatient physician, these complicated cases necessitate a multidisciplinary approach by the coordinated care of intensivists, infectious disease specialists, neurologists, cardiologists, and cardiac surgeons.^{25,26}

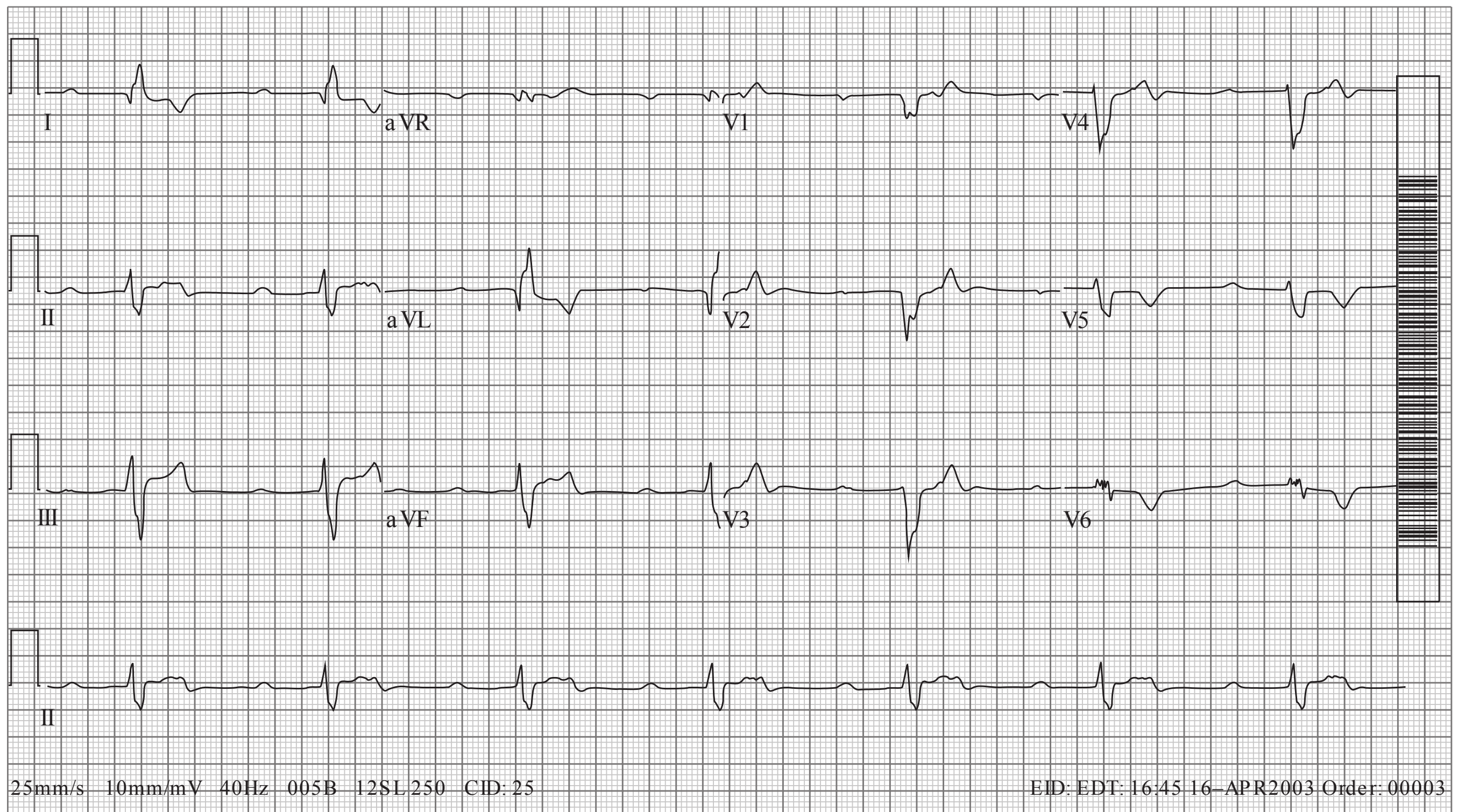


FIGURE 47-6 EKG: second-degree heart block (2:1 conduction) with a ventricular conduction delay due to *Staphylococcus aureus* endocarditis of the aortic valve with a ring abscess in a hemodialysis patient. The patient progressed to third-degree block, requiring temporary transvenous pacing.

Drug Users

The incidence of IE in IVDA is 1.5 to 20/1,000 addicts, with 80% involving the right heart as compared with only 9% right heart infection in non-IVDA native valve IE patients. This high proportion of right-sided disease in drug users is thought to result from microscopic endocardial damage due to impurities in illicit drug preparations and repeated bacteremia from unsterile injections. The most frequent underlying cardiac abnormality that predisposes IVDA patients to IE is a previous episode of IE. Right-sided IE is also associated with cardiac pacing and implanted defibrillators, in which the vegetations are usually confined to the leads but there is tricuspid valve involvement in 10% of cases.^{7,17,19}

Prosthetic Valve

Prosthetic valve endocarditis (PVE) accounts for up to one quarter of all IE cases; the percentage has been increasing as more valve replacements are performed. The risk of IE for patients with prosthetic valves is 1% at 1 year and 2% to 3% at 5 years. The early risk is higher with mechanical valves than for biologic valves, but the risk appears to become equivalent later in the postoperative period. PVE of mechanical valves typically has involvement of the cusps, sewing ring, and valve annulus, while with biologic valves the infection is mostly limited to the cusps.^{2,5,7}

Nosocomial Endocarditis

A relatively new category of endocarditis is nosocomial IE (NIE), defined as occurring greater than 48 hours after hospital admission or within 4 to 8 weeks of an invasive procedure performed in the hospital, which includes early prosthetic valve infections. The incidence of NIE is estimated to be 0.8 per 10,000 hospital admissions, and it accounts for 14% to 25% of all IE cases. Considered a subset of NIE is ICU-acquired IE, which has an estimated incidence of 5 per 1,000 ICU admissions. Elderly (age > 65) patients more often develop NIE than do younger (age < 65) patients and have twice the inpatient mortality; their risk factors are diabetes mellitus, and GI or GU cancers. The source of infection is a central venous catheter in 9% to 48% of cases, a peripheral venous catheter in 6% to 22% of cases, a pulmonary artery catheter in 2% to 9% of cases, and GU tract surgery or instrumentation in 20% to 30% of cases. *S. aureus* is the most prevalent microbe, causing 52% to 57% of cases (an intravascular device is the source in 91% of these patients); 13% to 25% of hospitalized patients experiencing staphylococcal bacteremia will develop IE. Coagulase-negative *Staphylococcus* causes 40% of cases (associated with prosthetic valves in 89%), *Enterococcus* species causes 5% to 30% of cases, and GNB cases are rare except for *P. aeruginosa* in hemodialysis patients. This organism has the capability to adhere to endocardium, unlike most GNB that are often responsible for bacteremia

and sepsis, but not IE due to low adherence factors. Although fungal NIE is still relatively rare (less than 10% of all IE cases), its incidence is increasing. The hallmarks of fungal IE are bulky vegetations with emboli to major arteries.^{11,14,16}

DIAGNOSIS

Previous diagnostic criteria for IE, such as the Von Reyn criteria, have been replaced by the more sensitive and specific Duke criteria, which include echocardiographic data that previously were not included. Recent updates to the Duke criteria have made evidence of *S. aureus* bacteremia a major criterion. For suspected cases of IE, at least three sets of blood cultures should be done at individual venipuncture sites during the first 24 hours after presentation; there should be at least 1 hour between first and last sets being drawn. This protocol is intended to reduce the chance of identifying contaminated samples while enhancing the ability to detect persistent bacteremia, the hallmark of IE. Only 5% to 7% of patients not recently on antibiotics have negative blood culture results. In these patients, antibiotic binding resins can be used to enhance the culture yield and polymerase chain reaction (PCR) testing can be done on vegetation or embolic samples, since PCR will yield positive results even after several weeks of antibiotic treatment.^{1,2,27}

ECHOCARDIOGRAPHY

Transthoracic echocardiography (TTE) has a sensitivity of 46% to 65% for detecting left-heart vegetations as compared with 90% to 93% for transesophageal echocardiography (TEE). The sensitivity for detecting left-heart regurgitation is also 58% to 63% for TTE and 88% to 98% for TEE, but the two modalities are equal for detecting right-heart IE. The risk of a false-negative study TTE is increased by obesity, COPD, prosthetic valves, and vegetation size < 5 mm. TTE is often of limited utility in the ICU due to restrictions on patient positioning, surgical wounds interfering with optimal ultrasound probe contact, and mechanical ventilation resulting in poor image resolution. Based on these data, it is considered reasonable for low-risk suitable patients to have a TTE as an initial study but to use TEE for high-risk or complicated patients, including any suspected PVE. Although there are pathognomonic echocardiographic findings, such as leaflet perforation, periannular or myocardial abscess, or new prosthetic valve dehiscence, neither mode can reliably differentiate the classic sonographic finding of IE, an oscillating intracardiac mass representing a vegetation (see Figure 47-7), from other non-infective lesions such as tumors, thrombus marantic endocarditis, or myxomatous valvular degeneration. Other diagnostic tests that are considered helpful in IE are a chest radiograph, an electrocardiogram, and urinalysis.²⁸⁻³⁰

MEDICAL TREATMENT

The treatment for IE is based on the principal of sustained antimicrobial activity with high serum concentrations in

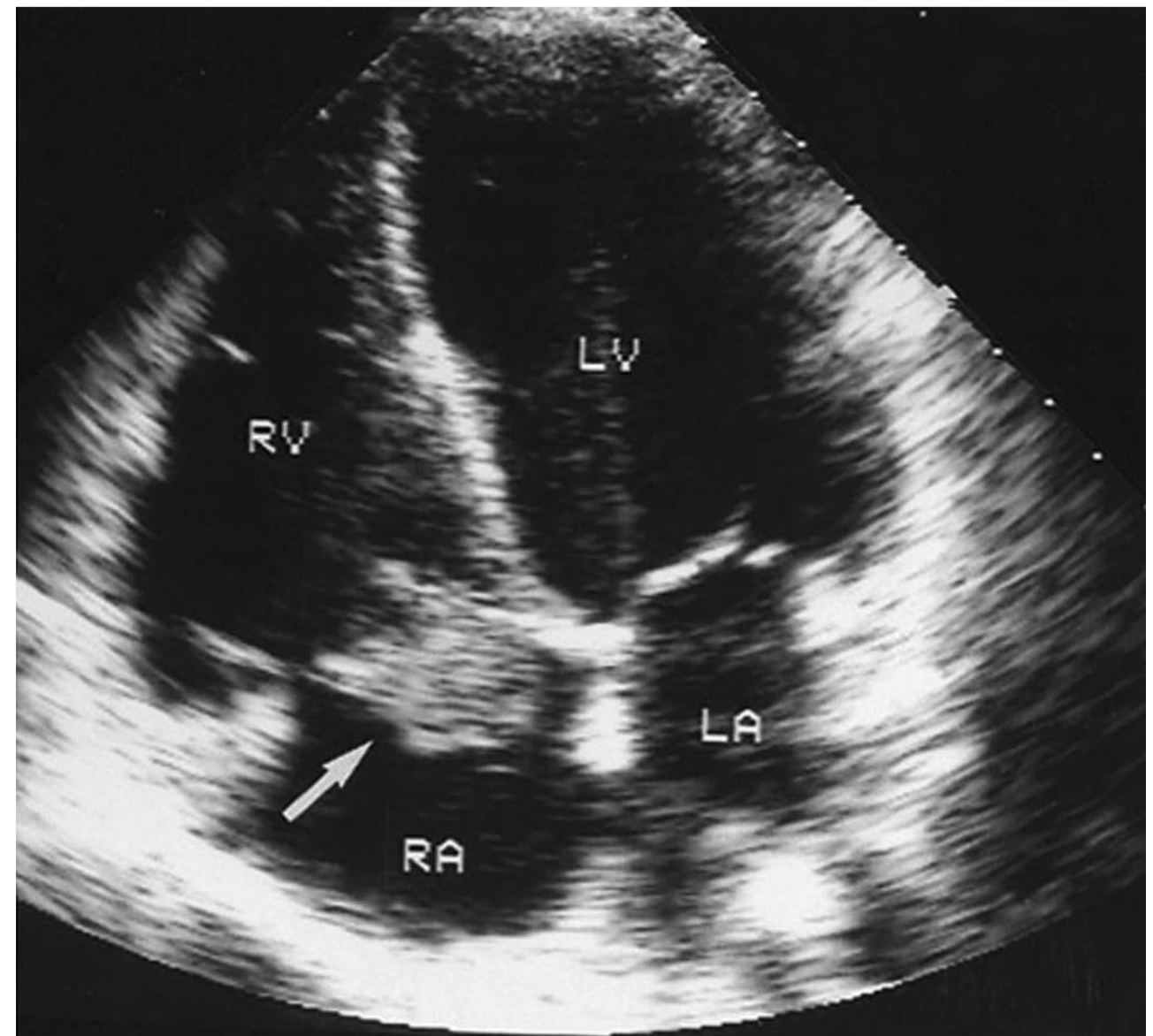


FIGURE 47-7 Apical four-chamber view demonstrating a large tricuspid valve vegetation (arrow). LA, left atrium; LV, left ventricle; RA, right atrium; RV, right ventricle. (Reproduced with permission from Fuster V, O'Rourke RA, Walsh RA, et al: *Hurst's the Heart*, 12th edition. New York: McGraw-Hill Inc; 2008.)

order to eradicate dormant microbes in vegetations and distant emboli. Prolonged IV bactericidal antibiotic regimens are the standard treatment. Blood cultures should be drawn every 24 to 48 hours after initiation of therapy until cultures are negative; this result marks the beginning of the time course of the regimen. Initial antibiotic regimens are described for the distinct patient population and should be adjusted based on microbe sensitivity and minimum inhibitory concentration. An initial choice of a cell-wall active drug (β -lactam or vancomycin) plus an aminoglycoside will give synergistic coverage against *Staphylococcus*, *Streptococcus*, and *Enterococcus* species that account for over 80% of all IE; this strategy has been shown to reduce the duration of bacteremia but not to change clinical outcomes.^{2,4}

Streptococcus viridans IE cases typically respond clinically to antibiotic treatment more quickly than does IE due to *S. aureus* or *Enterococcus*. For IE due to less virulent organisms, fever often resolves after 2 to 5 days of appropriate antibiotics. Persistent fever beyond the first week of treatment often indicates complicated disease, while recurrence of fever in weeks 3 to 4 is more often due to drug hypersensitivity, particularly with high β -lactams, but emboli may still occur. All patients should receive their first 2 weeks of therapy as inpatients to monitor for complications during this highest-risk period. Stable patients without complication may be considered for outpatient IV therapy to complete their regimen after this time. There is no benefit of additional oral antibiotics after completing a full IV course. Follow-up cultures should be done to ensure treatment success without relapse that most commonly occurs within 2 months of the conclusion of the antibiotic regimen. The relapse, or treatment failure rate,



TABLE 47-1: Disease Prevention: Endocarditis

Organization (Date)	Population	Recommendations	Comments	Source
AHA (2007)	Persons at highest risk for adverse sequelae from endocarditis ^a	Give antibiotic prophylaxis ^b before certain dental ^c as well as certain other procedures ^d	<ol style="list-style-type: none"> 1. New emphasis is on providing prophylaxis to patients at greatest risk of complications of endocarditis, rather than at greatest lifetime risk of endocarditis. 2. General consensus suggests few cases of infective endocarditis can be prevented by preprocedure prophylaxis with antibiotics. 	<i>Circulation.</i> 2007;116:1736

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^aPatients with prosthetic valve, previous endocarditis, selected patients with congenital heart disease (unrepaired cyanotic CHD, completely repaired congenital heart defect with prosthetic material or device during first 6 months after procedure, repaired cyanotic CHD with residual defects at or near repair site), and cardiac transplant recipients who develop valvulopathy.

^bStandard prophylaxis regimen: amoxicillin (adults 2.0 g; children 50 mg/kg orally 1 hour before procedure). If unable to take oral medications, give ampicillin (adults 2.0 g IM or IV; children 50 mg/kg IM or IV within 30 minutes of procedure). If penicillin-allergic, give clindamycin (adults 600 mg; children 20 mg/kg orally 1 hour before procedure) or azithromycin or clarithromycin (adults 500 mg; children 15 mg/kg orally 1 hour before procedure). If penicillin-allergic and unable to take oral medications, give clindamycin (adults 600 mg; children 20 mg/kg IV within 30 minutes before procedure). If allergy to penicillin is not anaphylaxis, angioedema, or urticaria, options for nonoral treatment also include cefazolin (1 g IM or IV for adults, 50 mg/kg IM or IV for children), and for penicillin-allergic oral therapy includes cephalexin 2 g PO for adults or 50 mg/kg PO for children.

^cAll dental procedures that involve manipulation of gingival tissue or the periapical region of teeth or perforation of oral mucosa.

^dAntibiotic prophylaxis may be reasonable for procedures in the respiratory tract or infected skin, skin structures, or musculoskeletal tissue. Antibiotic prophylaxis solely to prevent endocarditis is *not* recommended for GU or GI procedures.

is < 2% for *S. viridans*, 8% to 20% for *Enterococcus*, and 11% for *S. aureus*. There is no proven benefit of preventing emboli by giving aspirin or heparin, and since these agents increase the risk of intracranial hemorrhage, they should be avoided. Anticoagulation can be used judiciously for a prosthetic valve patient, but it should be held for 2 weeks if an embolic CNS event occurs.^{2,4,12} Systemic anticoagulation is generally contraindicated with IE, especially when caused by *S. aureus*, due to the high risk of intracranial hemorrhage, even when no CNS emboli are recognized since occult bleeding may occur.³¹ Antiplatelet therapy for patients with cardiac and cerebrovascular disease, such as recent coronary stents or ischemic stroke, should be continued during IE if there has been no intracranial hemorrhage.²²

SURGICAL TREATMENT

Although there have not been any controlled studies, it does appear that combined medical and surgical treatment yields a better outcome than medical treatment alone for complicated left-sided IE, particularly if *S. aureus* is the cause. More than 25% of all IE patients receive cardiac surgery during their acute illness and 20% to 40% receive it later. Despite the goal of sterilizing the tissue of the surgical field prior to procedure, there is little correlation between length of preoperative antibiotics and outcome. It may be a more productive goal of performing valve surgery early to prevent the possible complications that may occur and thereby increase the operative risks. The strongest indications for surgical treatment or either right- or left-sided IE are CHF due to acute valvular dysfunction or prosthesis dehiscence, prosthetic valve obstruction, periannular or myocardial abscess, mycotic aneurysm, fungal IE, or *S. aureus* PVE. Combined medical and surgical therapy

lowers the mortality rate of NVE patients with moderate to severe CHF to 11% to 35% as compared with 56% to 86% with medical therapy alone. Persistent bacteremia after 1 week on appropriate antibiotics or ongoing systemic emboli are also considered indications for surgical treatment. For right-sided IE, an additional surgical indication is tricuspid valve vegetation > 20 mm.³² Unstable septic shock or severe uncorrected coagulopathy is a contraindication for valve surgery. Operative mortality is significantly higher if pulmonary edema or cardiogenic shock due to valvular dysfunction has developed. If the patient has had an ischemic CNS embolic event, surgery can be done early (within 72 hours) in efforts to prevent further emboli, or surgery should be delayed 2 to 3 weeks to decrease the risk of hemorrhagic transformation due to heparin exposure. It is recommended to delay surgery for a minimum of 4 weeks after an intracranial hemorrhage. These recommendations to postpone surgery are valid only if CHF or cardiogenic shock has not developed. Tricuspid valvectomy without replacement is highly effective treatment for IE, but invariably leads to severe and permanent right ventricular dysfunction. The postoperative antibiotic regimen should complete a full course or be at least 7 to 15 days if the valve cultures are negative. If the valve cultures are positive, then a full antibiotic course should be given starting at the date of surgery.³³⁻³⁹

MORTALITY

While the overall inpatient mortality is 16% for all IE cases, there is quite a range in mortality depending on the disease category. The mortality is 26% for complicated left-sided NVE, 44% for PVE, 45% to 54% for IE patients requiring ICU admission, and highest at 68% for NIE. The lowest-risk

mortality at < 10% is in IVDA with isolated right-sided disease. Factors indicating a poor prognosis are CHF, septic shock, CNS events, acute renal failure, immunocompromise, higher Acute Physiology and Chronic Health Evaluation (APACHE) II score, and *S. aureus* as the infectious agent.^{2,4,5,26}

PROPHYLAXIS

New recommendations for IE prophylaxis have limited treatment for the highest-risk groups (see Table 47-1): prosthetic valves, previous IE, valvulopathy after cardiac transplant, complex cyanotic congenital heart disease, and surgical systemic-pulmonary shunts. They also limited the procedures requiring prophylaxis to gingival or periapical dental work, or incision through infected skin or soft tissue.³⁹

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Clostridium Difficile Infection

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Clostridium difficile Infection (CDI) is the most common cause of infectious nosocomial diarrhea in adults in developed countries. Currently, it is considered an important transmissible nosocomial disease causes often appear in outbreaks within healthcare facilities. Prior to 1977, the clostridial disease most commonly described was a form of skin and soft-tissue gangrene caused by a strain named *Clostridium perfringens*, with fatal outcomes often reported. Once the antibiotic era started, an antibiotic-associated colitis was first described in animal models caused by *Clostridium difficile* (*C. difficile*). Shortly after, *C. difficile* associated colitis became the most common clostridial infection among humans in the hospital setting.¹⁻⁴

Currently, CDI is not a reportable disease in the United States. For this reason, the exact incidence in the United States is difficult to establish. Nonetheless, it has been reported that there are at least 500,000 cases in US hospitals and long-term care facilities per year that result in 30,000 deaths. Surveys conducted in different Canadian hospitals between 1997 and 2005 suggest rates ranging from 3.4 to 8.4 cases per 1,000 admissions.^{5,6} The annual cost spent on patients with CDI in the United States exceeds 1 billion dollars, which is expected to trend up in the next few years given the high burden of recurrent disease.⁷ The number of patients discharged from the hospital and transferred to long-term care facilities with the diagnosis of CDI doubled between 2000 and 2003.

It is well known that the vast majority of patients diagnosed with CDI had previous exposure to antibiotics, especially within the 28 days prior to the onset of symptoms—hence, the name *antibiotic-associated colitis*, which has been proven to be sufficient to support the current effort to restrict the indiscriminate use of antibiotics as part of infection control interventions.

MICROBIOLOGY AND PATHOGENESIS

The genus *Clostridium* includes more than 200 species of anaerobic, gram-positive, rod-shaped bacteria, capable of forming spores and responsible for toxin-mediated pathogenic processes, which can cause a broad spectrum of invasive diseases. The name *Clostridium difficile* comes from the Greek word *Kloster*, meaning spindle. When *C. difficile* was first described, it was particularly difficult to isolate the bacillus, which is the reason why it was initially named *Bacillus difficilis*. However, posterior ribosomal DNA analysis proved morphologic similarities with some strains from the genus *Clostridium*, such as *Clostridium sordellii*; then, it was renamed *Clostridium difficile*.⁸

Clostridia produce an important number of biologically active proteins, such as hemolysins, proteolytic enzymes, and—most important—toxin proteins. Toxin production, which is controlled at the transcriptional level by a *sigma* factor, includes neurotoxins, enterotoxins, necrotoxins, collagenases, proteases, and neuroaminidases. These toxin molecules account for most of the pathogenic and lethal potential in humans.¹

Clostridium species are usually found in soils and are part of the intestinal microbiome in healthy humans. By the 1990s, over 70% of healthy humans were reported to be colonized with concentrations of 10^8 to 10^9 of *Clostridium* spp. per gram of feces.² This genus of bacteria tends to form spores that are able to survive and persist in hostile environments such as heat, desiccation, and disinfectants. The spores may also spread via aerosol transmission as part of dust clouds. In the case of *C. difficile*, it may also be acquired through direct contact with infected individuals or contaminated surfaces, equipment and clothing, as well as by fecal–oral transmission.¹

After the use of antibiotics, the intestinal microflora is disrupted, which is the first step in the pathogenesis of CDI. The concentration of intestinal ubiquitous bacteria decreases significantly with any type of antibacterial activity. However, *C. difficile* spores remain, resulting in rapid germination of new spores and, subsequently, *clostridia* overgrowth. The first virulent effect is the production of two toxins, an enterotoxin labeled toxin A and a cytotoxin labeled toxin B. Toxin A activates macrophages and mast cells, leading to an inflammatory cascade, increased mucosal permeability, and fluid secretion into the intestinal lumen, which ultimately will be manifested as diarrhea. On the other hand, toxin B mediates disruption of the tight junctions between intestinal epithelial cells, and is responsible for cell injury, cell death, and secondary worsening of the inflammatory response, which will be clinically evident with a highly elevated white blood cell (WBC) count.⁸ Toxin B has 10 times more impact on the gastrointestinal (GI) mucosa than toxin A.⁹ Cellular and mucosal damage eventually leads to focal ulceration and accumulation of purulent material, with necrotic debris that will be evidenced as pseudomembranous colitis macroscopically.¹⁰

Recently, a hypervirulent strain has been described, responsible for outbreaks of severe CDI. The strain is referred to as NAP1/BI/027 given the complexity of the methods used to detect its presence, including pulsed-field electrophoresis (NAP1), restriction endonuclease analysis (BI) and PCR (027). NAP1/BI/027 *C. difficile* produces a third toxin that is not present in other *C. difficile* strains and that is believed to account for antibiotic resistance given that it is resistant to fluoroquinolones in vitro; this was an infrequent observation in *C. difficile* strains prior to 2001. However, its exact role is not well understood.⁹ This novel strain is considered hypervirulent given its ability to produce substantially larger quantities of Toxins A and B in vitro when compared to other *C. difficile* strains. This is believed to be due to a partial deletion of the gene that encodes for Toxin C, which is responsible for the downregulation of toxin production. This may contribute to the enhanced production of Toxins A and B and its hypervirulent potential.

Lower clinical cure rates and increased recurrence rates have been observed among patients infected with this novel strain when compared with patients infected with non-hypervirulent *clostridia*.^{7,11} It has been associated with severe disease, severe outcomes (intensive care unit admission, toxic megacolon, colectomy) and increased mortality (death within 14 days).⁹

EPIDEMIOLOGY

Local incidence and prevalence of CDI may vary considerably depending on the antibiotic prescribing behaviors among clinicians in different areas of the country, and also, would correlate directly with the definition of antibiotic associated diarrhea from hospital to hospital.¹¹ In 2001, the number of patients discharged from the hospital with the diagnosis of CDI increased at a very rapid rate among the population older than 65 years old, with a 5-fold increase in the incidence in this age group when compared to the group aged

from 45–64 years old. By 2003, there was a 4-fold increase in the incidence in the general population when compared to the rates reported in year 1991. By 2005, the reported incidence of *C. difficile* colitis in hospitals and healthcare facilities was 84 cases per 100,000.^{11,12}

Epidemiology Basics

The molecular epidemiology of *C. difficile* is varied; one particular ribotype can predominate in a particular area during certain periods of time and, simultaneously, be extremely rare elsewhere.⁵ This has great clinical and epidemiologic importance, since different ribotypes have different treatment responses and are associated with different rates of morbidity and mortality.¹³

The incubation period from the time of exposure to the development of symptoms is not very well known. Some reports estimate it between 2 and 3 days; other sources say up to 7 days.

The organism manifests itself in two different ways: carrier state, which is also known as colonization, or symptomatic state, also known as infection.

C. difficile colonization occurs when a patient exhibits no clinical symptoms and tests positive for the organism and/or its toxin. On the other hand, *C. difficile* infection occurs when a patient exhibits clinical symptoms and tests positive for the organism and/or its toxin. Studies suggest that asymptomatic carriers may be an important reservoir of *C. difficile* in healthcare settings. However, the data regarding their role is conflicting. A recent study done at Barnes-Jewish Hospital enrolled patients without diarrhea from June 2010 through October 2011 and examined their stools. Results showed high prevalence of toxigenic *C. difficile* (TCD) colonization on admission. However, in contrast to past studies, it was not associated with recent antimicrobial or healthcare exposures. Additional investigation is needed to determine the role of asymptomatic TCD carriers in the hospital setting.¹⁴

Community Acquired Versus Hospital Acquired Infection

Community-acquired *C. difficile* infection (CA-CDI) is an increasingly reported condition. It is being described in populations lacking the traditional predisposing factors that were previously considered at low risk for this condition.¹⁵

The factors responsible for the emergence of CDI in the community are not clear, but could be related to the emergence of novel risk factors, the epidemic hypervirulent *C. difficile* strain, food and water contamination, and/or an increase in the proportion of asymptomatic carriers in the community, which would lead to an increase in person-to-person transmission.⁹

CLINICAL MANIFESTATIONS

Several risk factors for CDI have been identified and sorted in three groups:

Environmental risk factors favoring exposure to *C. difficile* spores

- High colonization rate
- Prolonged hospital stay
- Admissions to the intensive care unit
- Sharing a room with an infected patient
- Being hospitalized in a room just after an infected patient

Risk factors favoring colonization of the digestive tract

- Antibiotic exposure (up to 6 months prior to symptom onset)
- Chemotherapy
- Proton pump inhibitors (PPIs)
- Nasogastric and orogastric tubes
- Gastrointestinal or intra-abdominal surgery
- Anti-acids
- Enemas
- Laxatives

Host-related risk factors

- Age more than 65 years
- Comorbidities
- Immunosuppression or decreased host immune response (decreased rate of neutralizing antibodies)
- Women more than men
- Previous CDI episode

However, recent reports have documented that CDI is occurring among patients without traditional risk factors. A recent cohort study among patients admitted to Sunnybrook hospital in Toronto, Canada from June 1, 2010 through May 31, 2012 demonstrated that CA-CDI is occurring among populations not traditionally considered high risk (i.e., young age, people without underlying illnesses, no history of exposure to hospitals or to antimicrobials). Their results showed that the incidence rates of CA-CDI and HA-CDI were similar.¹⁶

The different clinical presentations of CDI range from mild diarrhea to severe colitis. The factors that influence

the variation of presentations are not well understood; it is thought that the host's immune response determines both the presentation and outcome.

Authors of clinical studies have indicated that antitoxin responses in both serum and intestinal secretions could prevent CDI, whereas an inadequate immune response or low titers in serum antibodies could be correlated with the occurrence of a first CDI episode or recurrent *C. difficile* diarrhea.⁸

Clinical Definitions

The clinical spectrum ranges from no symptoms to fulminant colitis. Diarrhea may be present in almost every case, but in some patients may be initially absent. A very detailed history, emphasizing prior exposure to antibiotics or admissions to healthcare facilities over the previous 3 to 6 months, is very important information.

Three important factors are to be taken into account when classifying the CDI episode: age, leukocytosis, and serum creatinine (Figure 48-1).

A greater age is related to adverse outcomes given its association with senescence of the immune response against *C. difficile* and its toxins. The level of leukocytosis likely reflects the severity of colonic inflammation; complications are more common among patients with a WBC of 15,000 cells/mL or higher than among patients with a normal WBC. The course of the disease is truly catastrophic in patients with WBC of 50,000 cells/mL or higher. On the other hand, an elevated serum creatinine level may indicate severe diarrhea with subsequent dehydration or inadequate renal perfusion.^{17,18}

Diarrhea with colitis may present as watery diarrhea up to 10 or 15 times daily with lower abdominal pain and cramping. Fever (temperature more than 38.5°C) is a sign of severe *C. difficile*-associated diarrhea (CDAD); this is reported to routinely be associated with a WBC of 15,000, on average. These symptoms may begin during the antibiotic therapy or 5 to 10 days following antibiotic administration. Infrequently, symptoms present as late as 10 to 24 weeks after cessation of therapy.

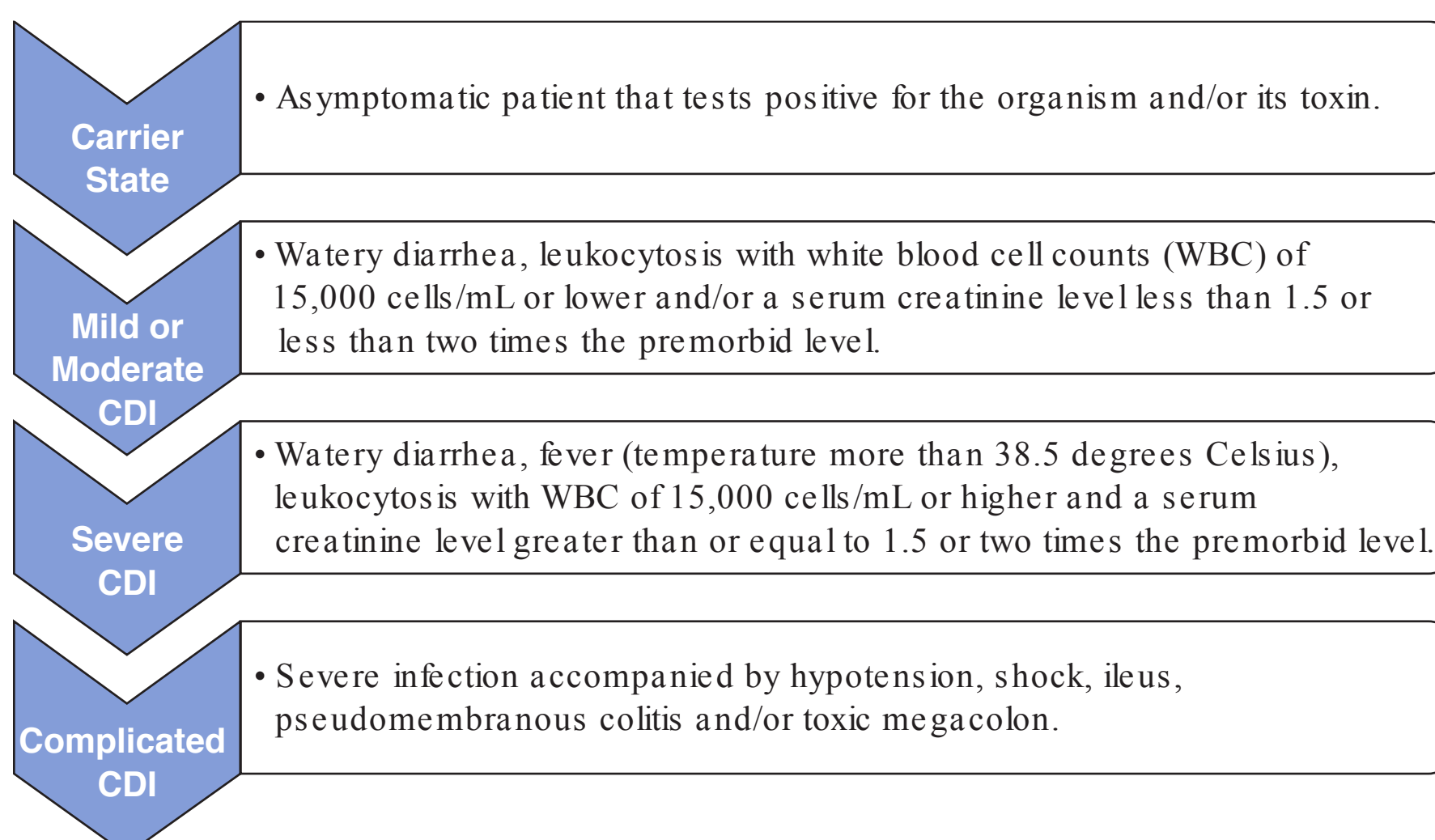


FIGURE 48-1 CDI Classification.

Physical examination generally demonstrates lower abdominal tenderness.¹⁸ Unexplained leukocytosis in hospitalized patients (even in the absence of diarrhea) may reflect underlying *C. difficile* infection. The complications include fulminant colitis, toxic megacolon, colonic perforation, and septic shock.

Associations with Other Gastrointestinal Conditions

It is sometimes difficult to distinguish between an inflammatory bowel disease (IBD) flare and an episode of CDI; in some cases, they may either coexist or one could present as a consequence of the other. High index of suspicion for CDI should be raised for patients with known risk factors. A prompt diagnosis and treatment should be sought given that patients with IBD may not develop pseudomembranes, even in severe infections, in which case the episode of CDI is masked by its atypical presentation.¹⁹ A delay in treatment could increase the risk of complications and mortality.

Protein losing enteropathy has been described as a consequence of mucosal inflammation, especially in recurrent disease. Appendicitis has also been described in the literature; however, it is extremely infrequent.²⁰

Extraintestinal Manifestations

Bacteremia, reactive arthritis, pancreatic abscesses, cellulitis, necrotizing fasciitis, osteomyelitis, and prosthetic device infections have also been described.²¹

Recurrent Disease

Recurrent disease accounts for reinfection with a new strain or relapse of a prior infection with the same strain. Without genetic studies, it is almost impossible to distinguish these two entities. In clinical practice, the significance of differentiating one from another is unclear, since the management remains the same. However, it is important to recognize the phenomena of recurrences, in order to implement the appropriate treatment, which differs between the therapy offered for a first episode or a first recurrence.

Low serum concentrations of antibodies directed against Toxins A and B (anti-TcdA and anti-TcdB) have been associated with a higher risk of recurrence of CDI after successful antibiotic treatment. A recent study compared the results for patients without a subsequent recurrence with those of patients who suffered from a relapse within 60 days after completing the first antibiotic regimen. Advanced age, comorbidities, and low serum levels of anti-TcdA and anti-TcdB antibodies were associated with recurrent disease.²²

Other studies have shown that recurrent CDI is hallmarked by greater numbers of circulating CD3-positive lymphocytes skewed toward a Th1/Th17 inflammatory population, as well as possible immune plasticity.⁸



FIGURE 48-2 Significant dilatation of the colon. Presence of ileus.

DIAGNOSIS

The clinical manifestations, when highly suggestive, are sufficient enough to make a presumptive diagnosis and start empirical treatment. In 2010, the Infectious Disease Society of America (IDSA) and the Society for Healthcare Epidemiology of America (SHEA) published the *Clinical Practice Guidelines for Clostridium difficile Infection in Adults*.⁴ Later in April 2013, The American College of Gastroenterology published the most recent *Guidelines for Diagnosis, Treatment and Prevention of Clostridium difficile Infections*, in which they address the diagnostic and testing strategies for CDI.²³

Abdominal X-ray may show a distended colon and sometimes evidence of toxic megacolon. However, there are no significant X-ray findings for early and uncomplicated disease (Figure 48-2). Computerized tomography (CT) scan of the abdomen may be helpful in distinguishing findings such as pancolitis (Figure 48-3) and pseudomembranous colitis is

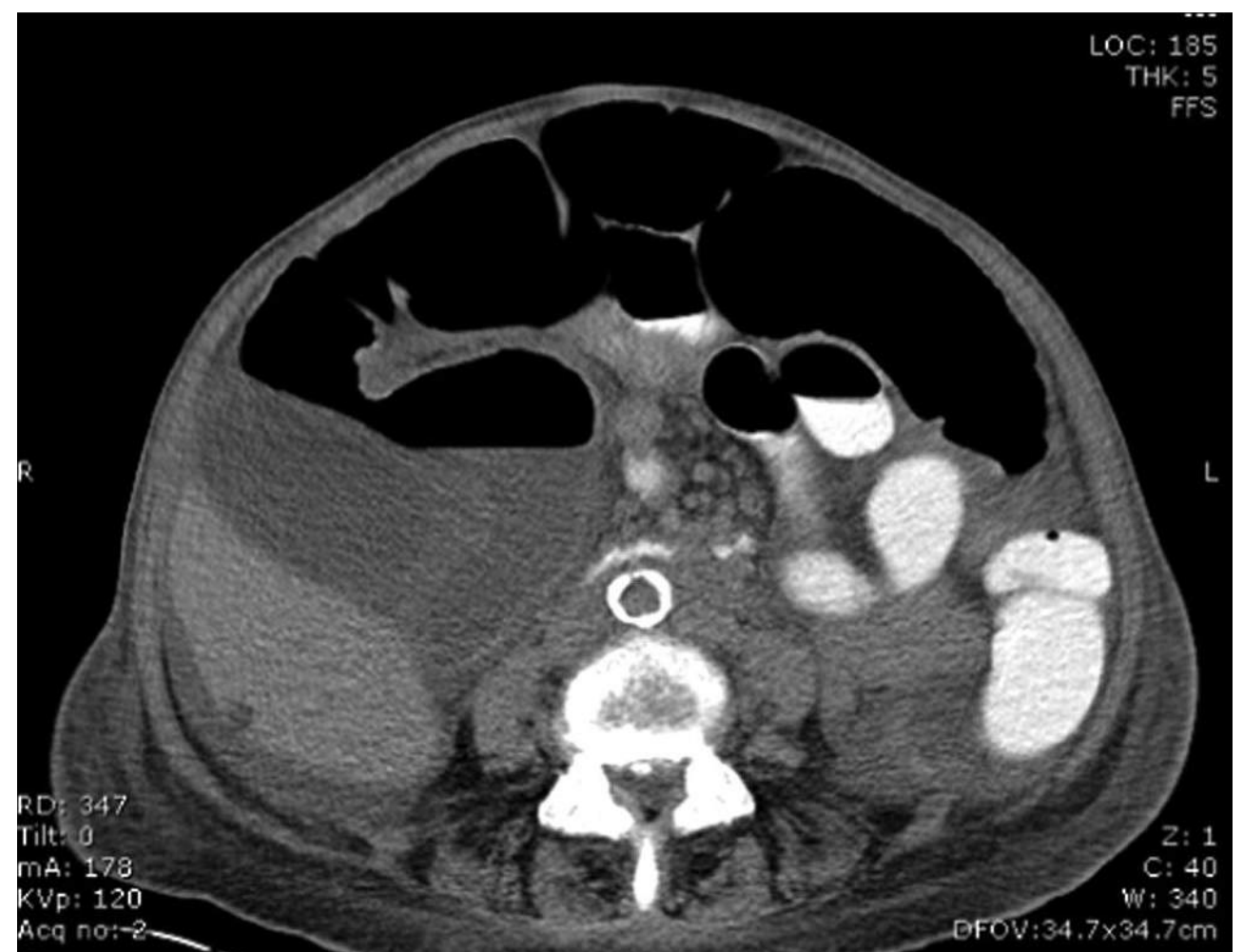


FIGURE 48-3 Pancolitis that is more evident in the descendent colon, with significant surrounding stranding and free fluid. Transverse and cecum distended with air.

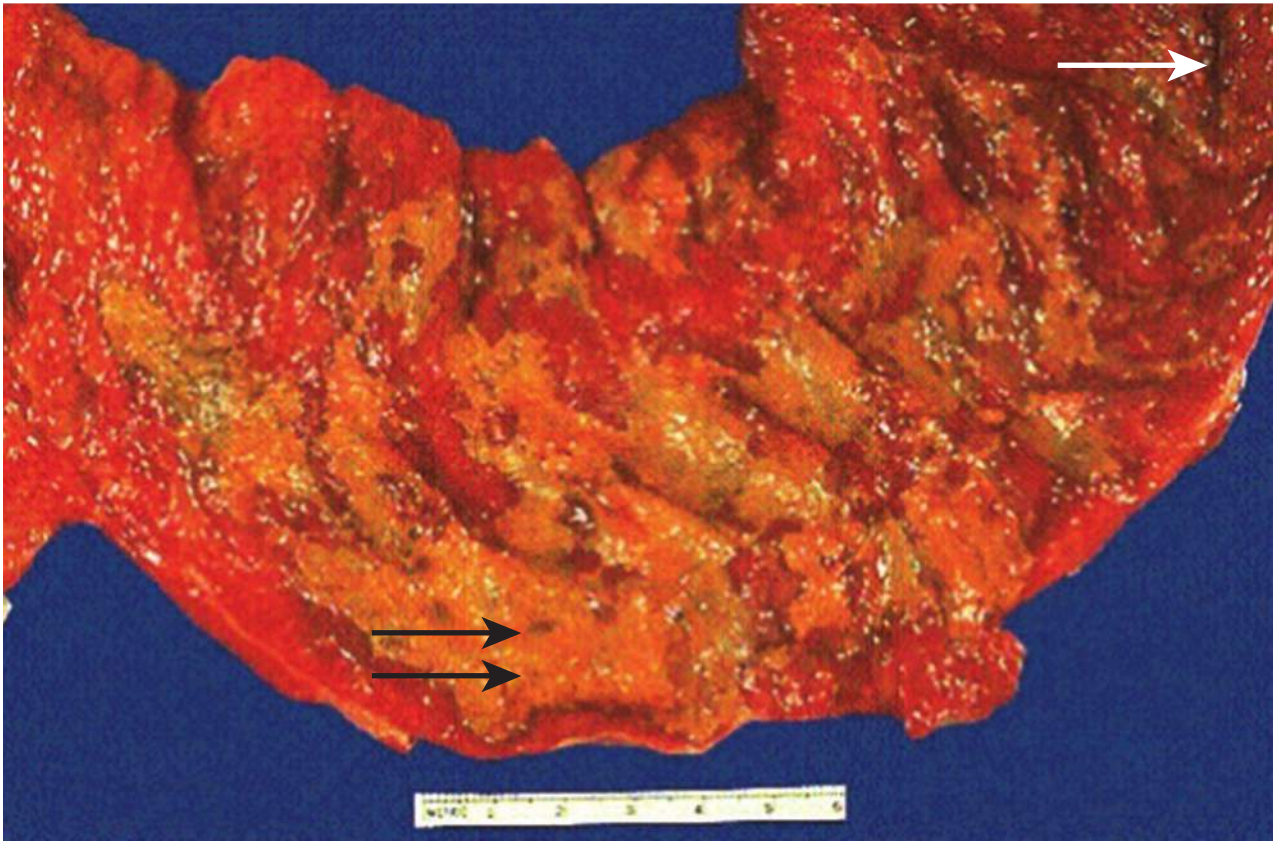


FIGURE 48-4 Macroscopic examination reveals the variegated appearance of the colonic mucosa due to the alternating areas of ulceration (*single arrow*) and membranous-like deposition of necrotic debris (*double arrow*).

diagnosed by sigmoidoscopic examination, with evidence of pseudomembranes that are pathognomonic of this disease (Figures 48-4 to 48-7).

Only stools from patients with diarrhea should be tested for CDI and testing stools from asymptomatic patients is not clinically useful. Cases of ileus and complicated disease that present with formed stools are very rare. Rectal swabs for PCR could be of use in these special situations but should not be used routinely for diagnostic purposes.

Diagnostic testing for CDI has evolved dramatically over the past 30 years. More than 10 years ago, the toxigenic cultures and the *C. difficile* cytotoxin neutralization assay (CCNA) were the two primary diagnostic tests. Stool *C. difficile* culture has been proven to have no diagnostic use because it does not differentiate between toxigenic and nontoxigenic organisms. Since only toxigenic organisms produce disease, specific toxigenic cultures were developed, currently being the most sensitive test. However, availability is limited;

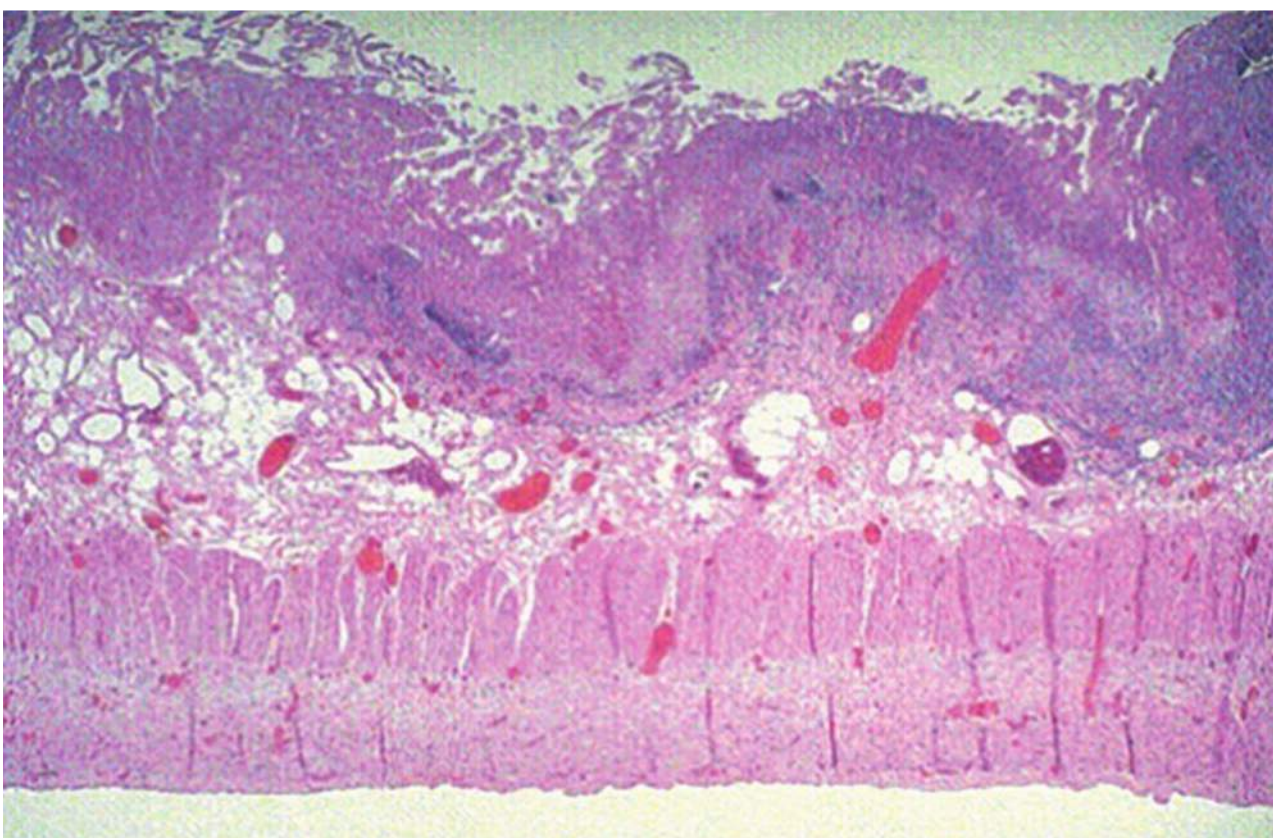


FIGURE 48-5 Scanning magnification reveals total denudation of the colonic mucosa with extensive replacement by fibrinopurulent exudate (H&E \times 400).

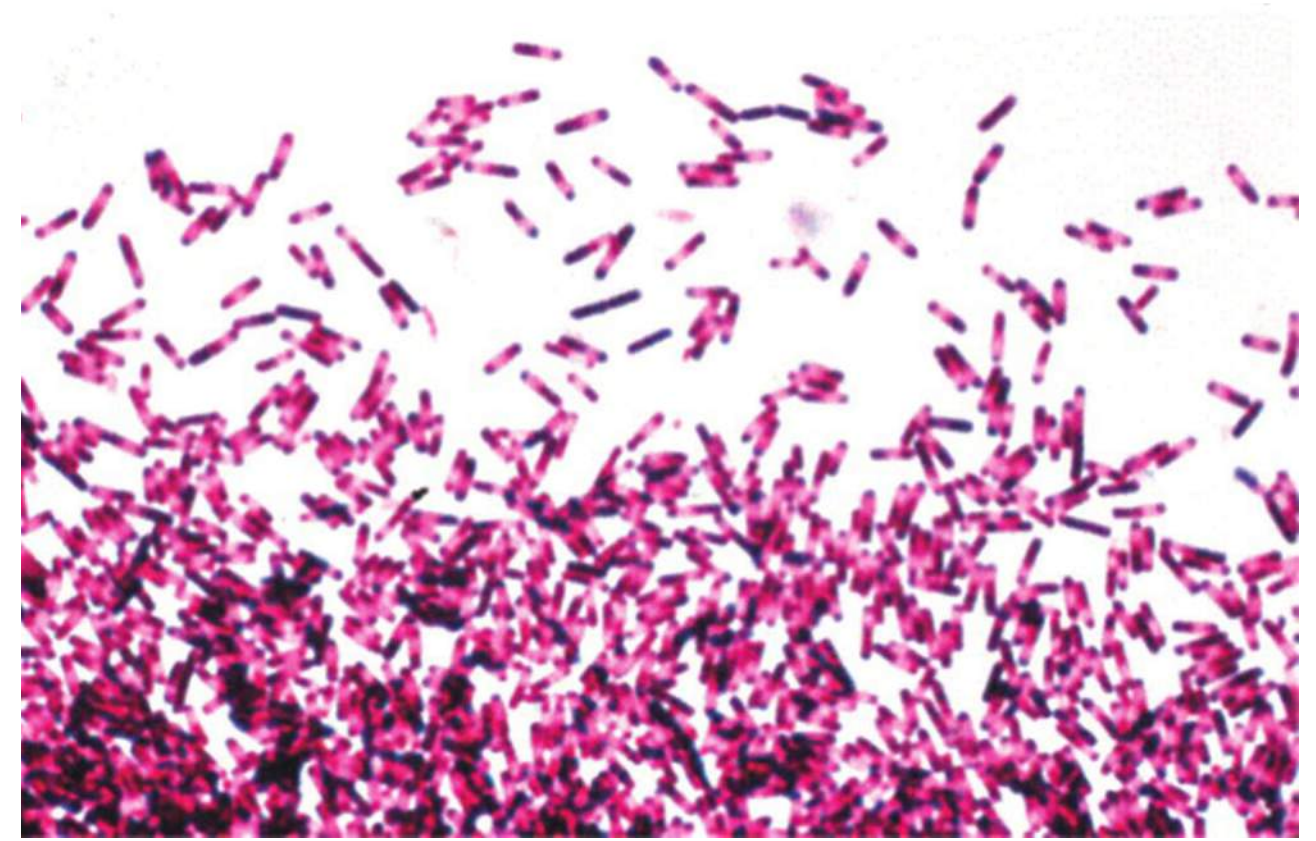


FIGURE 48-6 Oil immersion (\times 10,000) power of Gram stain from culture material shows *C. difficile* organisms with the characteristic uneven staining.

it is used only for epidemiologic purposes and is not clinically practical due to the slow turnaround time.²³

CCNA is a test designed to identify toxin B in the stool. Laboratory cells are exposed to a fecal sample presumed to be infected with *C. difficile*. This reaction triggers cellular damage and CDI is confirmed when an antibody against toxin B reverses the effects on these cells. This tool has high sensitivity and specificity, but its availability is also limited. Currently, it is only used as a reference standard with very low diagnostic value.²³

Glutamate dehydrogenase (GDH) is an enzyme produced by toxigenic and nontoxigenic organisms. Antibodies against GDH can be measured in serum. It is not specific and antibodies could cross-react with enzymes produced by other clostridial species. The actual value is more as a screening test, which, if positive, requires confirmation with nucleic acid amplification tests (NAAT).

Enzyme immunoassay (EIA) for *C. difficile* Toxins A and B is rapid but is less sensitive than the CCNA, and is

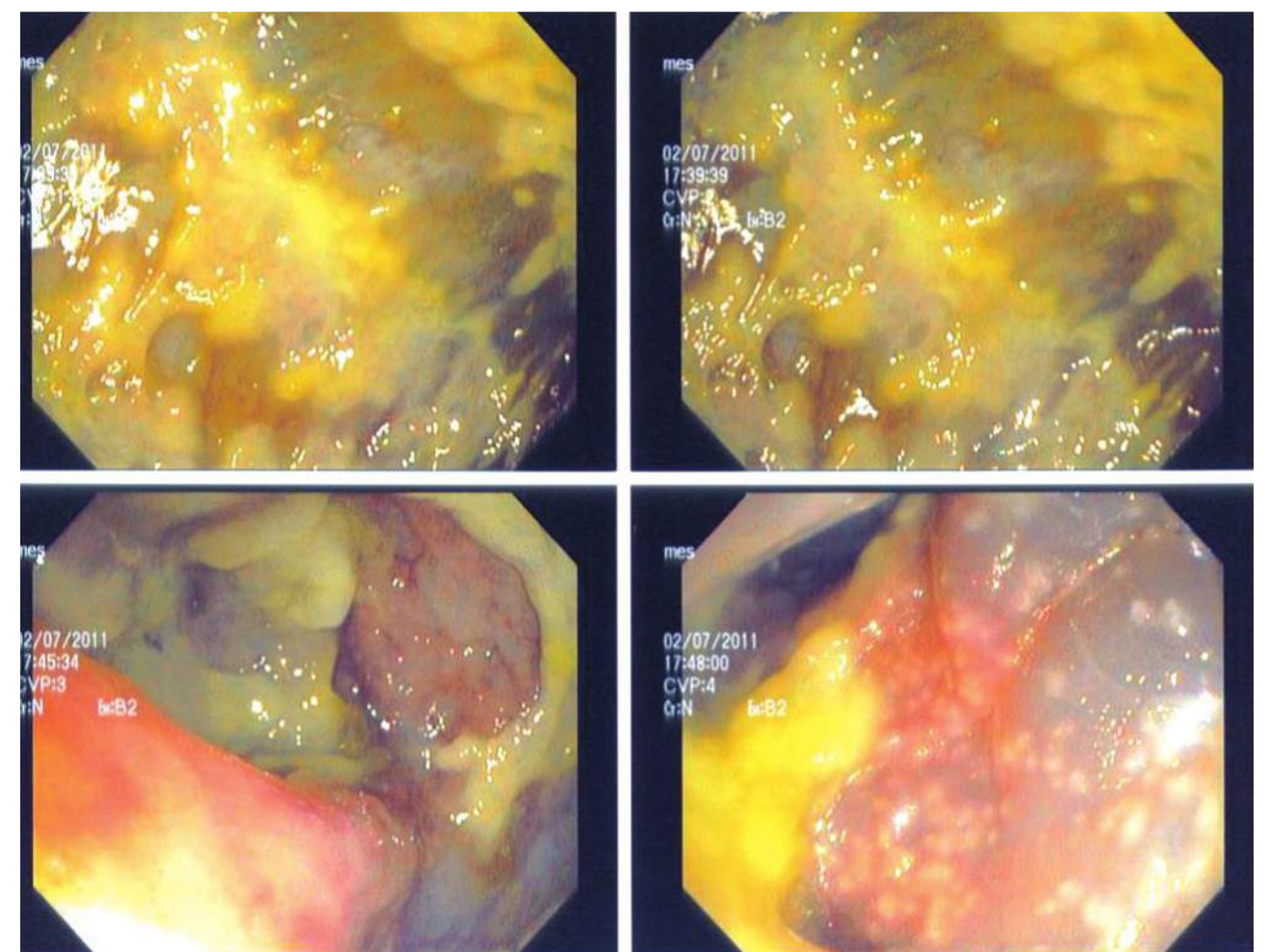


FIGURE 48-7 Severe *C. difficile* colitis. Edematous, gray, dusky, erythematous, thick pseudomembranes.

considered a suboptimal diagnostic approach for CDI. It is not recommended as a stand-alone test. The toxin A and B EIA has been adopted by more than 90% of the laboratories in the United States because of its ease of use and lower labor costs compared with the CCNA.²³

NAATs are good diagnostic tests when used alone, with high sensitivity and specificity. The Food and Drug Administration (FDA)-approved tools are the PCR assay and the loop-mediated isothermal amplification test (LAMP). However, more data for the LAMP test are needed at this time in order to recommend it as part of the guidelines.²³

Repeat testing with NAAT as well as testing for cure is strongly discouraged, given the high rate of false positives. Some of the tools, such as toxin A and B EIA, may remain positive in stool up to 30 days in asymptomatic patients and after completing treatment. Testing for cure could expose the patients to prolonged courses of antibiotics, which, paradoxically, might increase the risk for recurrence.²³

TREATMENT

The treatment modality has been stratified according to severity of the disease, as described in clinical manifestations (Figure 48-8).

Regardless of the severity, if a physician has a strong clinical suspicion for CDI, it is highly encouraged to discontinue any medications associated with CDI as triggering factors, if possible, and start empirical antimicrobial treatment regardless of the test results.

The first-line agents for treatment are metronidazole and vancomycin. Mild to moderate CDI may be treated with oral metronidazole 500 mg three times daily for 10 days. Severe CDI should be treated with oral or via nasogastric/orogastric tube vancomycin 125 mg four times daily for 10 days. Complicated CDI must be treated with oral or via nasogastric/orogastric tube vancomycin 500 mg four times daily plus intravenous metronidazole 500 mg three times daily for 14 days. In the presence of ileus, adding intracolonic administration of vancomycin 500 mg four to six times daily is encouraged, along with early surgical evaluation.

	<p>Mild to moderate CDI</p> <ul style="list-style-type: none"> • Oral Metronidazole 500 mg three times daily
	<p>Severe CDI</p> <ul style="list-style-type: none"> • Oral Vancomycin 125 mg four times daily
	<p>Severe Complicated CDI (early surgical opinion)</p> <ul style="list-style-type: none"> • Oral Vancomycin 500 mg four times daily plus IV Metronidazole 500 mg three times daily • Intracolonic administration of Vancomycin 500 mg four to six times daily should be considered in cases of ileus

FIGURE 48-8 Treatment guidelines.

In cases in which the use of metronidazole is contraindicated (i.e., pregnancy, breastfeeding, intolerance, anaphylaxis) vancomycin should be used as the preferred second-line agent.²³

In May 2011, the FDA approved a third agent currently used as a second-line therapy for mild to moderate disease. Oral or via nasogastric/orogastric tube fidaxomicin 200 mg two times daily for 10 days was proven to be noninferior to vancomycin. Unfortunately, there are a few publications already demonstrating strains of *C. difficile* that have developed increased minimal inhibitory concentrations when exposed to fidaxomicin. More data is needed at this time.²⁴

Antidiarrheal medications and PPIs should be avoided in patients with CDI given the high risk of masking the symptoms of complicated disease and their association with recurrent disease.

The risk of having a recurrence within the first 8 weeks after receiving treatment for an initial episode is 10% to 20%. Moreover, after a first recurrence, the risk of further recurrences rises up to 65%. In the event of a first recurrence, the same regimen used for the initial episode may be used. However, clinicians are encouraged to choose treatment modality according to the severity of the new episode. For the second recurrence, the treatment should be a tapered regimen of vancomycin.

A third recurrence is an indication to start fecal microbiota transplant (FMT), which is transferring fecal bacteria from a healthy donor into a patient with recurrent CDI in order to restore the normal colonic flora.¹⁸ An open-label, randomized, controlled trial by van Nood et al. in 2013 compared three different therapies; initial oral vancomycin regimen of 500 mg every 4 hours for 4 days followed by bowel lavage and FMT via a nasoduodenal tube; a standard oral vancomycin regimen of 500 mg every 4 hours for 14 days; and the same standard vancomycin regimen followed by bowel lavage only. Nasoduodenal FMT was significantly more effective for the treatment of recurrent disease than a vancomycin regimen.²⁵ A pilot study published in April 2014 compared nasogastric infusion of FMT with colonoscopic administration with a primary endpoint of resolution of the recurrent episode without further relapse within 8 weeks of treatment. Nasogastric administration was proven to be as effective as colonoscopic infusion.²⁶ In June 2014, Konijeti et al. designed a cost-effectiveness analysis that was published in the *Clinical Infectious Disease* journal, in which four different treatment modalities for recurrent CDI were compared: metronidazole, vancomycin, fidaxomicin, and colonoscopic FMT. The analysis concluded that initial (after the first recurrence) treatment with FMT via colonoscopy is the most cost-effective modality for management of recurrent CDI, and that in clinical situations for which FMT is not available, vancomycin was shown to be the most cost-effective strategy.¹⁵

Canadian physician surveys in Internal Medicine, Family Medicine, Gastroenterology, and Infectious Diseases revealed that 65% of clinicians that have taken care of patients with recurrent CDI have never offered, referred for, or even considered FMT. Among the different reasons, the most significant

is that physicians still do not recognize the indications for the therapy or consider they do not have the sufficient experience to recommend it. Of the respondents, 29% find the procedure unappealing enough to prevent them from offering the treatment to patients.²⁷ Innovative preparations of fecal inoculums and even synthetic encapsulated feces are under development, which may improve its acceptance by healthcare professionals and patients.

Over the course of the last two years, multiple probiotics have been studied in murine models. *Lactobacillus* species have shown to suppress the *C. difficile*-induced interleukin-8 from colonic cells, decreasing epithelial damage.²⁸ Spore formation from several *Bacillus* strains proved to decrease the severity of the symptoms²⁹ and novel multistrain probiotics may confer the host with protection against hypervirulent strains such as NAP1/BI/027.²⁰ Evidence in humans, although promising, is limited at this time and not routinely recommended.

Intravenous immunoglobulin (IVIG) has been used to treat severe CDI. The hypothetical mechanism of action is that an antitoxin A antibody binds and neutralizes toxin A.³⁰ It has been used to treat severe CDI given its strong correlation with low serum antitoxin antibodies. Patients with values of serum immunoglobulin G (IgG) less than 3.00 units were 48 times more likely to suffer from severe CDI when compared to healthy population.³¹ However, its role has only been anecdotal when used as adjuvant therapy, and evidence is controversial. Some studies suggest that the use of IVIG is limited in patients with severe CDI and extracolonic manifestations and the outcomes may become less beneficial.³²

Human monoclonal antibodies were proven to be effective in vitro and in early phases of clinical research trials. When analyzed as adjuvant therapy and compared with conventional therapy alone, they were associated with a 72% reduction in recurrences.³³ Evidence suggests that the human IgG1 has demonstrated to be the most effective and potent monoclonal antibody that is now promising for the future treatment of CDI.³²

Toxin-based vaccination and recombinant peptides against *C. difficile* have been investigated in depth in the United States. Formalin-detoxified toxins A and B, better known as toxoids, were obtained from a strain that is considered to be hyperproductive of both toxins. Mucosal and parenteral administration of these toxoids were tested and reported to be safe and fully immunogenic in murine models. These are currently undergoing clinical efficacy trials in humans.³⁴

Recombinant toxin subdomains or peptides have been designed to target epitopes associated with a main toxin domain. These epitopes will then enhance the production of neutralizing antibodies, maximizing the protective efficacy. Recombinant peptides are less cumbersome to produce, since the process of purification and detoxification is not required. When compared to toxoids, the risk of incomplete immunogenicity is almost nonexistent, and they seem to reduce the bacterial persistence within the host.^{35,36} There is also promising developing research in this realm.

Tigecycline has been used off-label in patients with severe CDI. Five successful cases were reported in the *Clinical*

Infectious Disease journal in 2009.³⁷ However, evidence is currently controversial. In 2014, the journal for *Antimicrobial Agents and Chemotherapy* published a study in which 10 days of treatment with Tigecycline were enough to shift the intestinal microbiome in mice and increase susceptibility to CDI for more than five weeks.³⁸ Tigecycline is currently not recommended for the treatment of *C. difficile*.

Rifaximin 400 mg twice daily has also been used off-label with a success rate of 86% in recurrent disease. However, there is strong evidence suggesting low thresholds for rifaximin resistance.³⁹

Ramoplanin is a glycolipodepsipeptide antibiotic and actagardine is a lantibiotic, both derived from the genus *Actinoplanes*. Ramoplanin-actagardine combinations were proven to be particularly effective to treat recurrent disease in human intestinal models. This combination offers an additive/synergistic effect for 62% of the strains brought under different antibiotic combinations.⁴⁰

Oritavancin is a novel glycopeptide antibiotic that proved to reduce the total *C. difficile* count to undetectable levels in murine and human gut models, without inducing spore germination or toxin production, unlike vancomycin. Oritavancin is now undergoing clinical trials in order to implement its use in severe CDI.⁴¹

Rifalazil is a benzoxazinorifamycin that blocks the β -subunit of the RNA polymerase in the bacterial genome. It has activity against *Mycobacterium tuberculosis* and other gram-positive bacteria. A study done in mice compared Rifalazil to vancomycin after *C. difficile* inoculation. The Rifalazil group had absence of epithelial cell damage, reduced intestinal wall edema, and less mucosal inflammatory reaction, unlike the vancomycin group, in which the mucosal damage and inflammation was evident. None of the Rifalazil-treated mice showed presence of toxins in stool after 30 days, which suggests that, in animal models, Rifalazil might be superior to vancomycin for the treatment of severe CDI. Investigation in humans is now under development for treatment of severe and recurrent CDI.⁴²

Novel inhibitors of the methionyl-tRNA synthetase known as REP3123 and second-generation lantibiotic recognized as NVB302 have demonstrated favorable in vitro effects against *C. difficile*, but more evidence in human models is warranted.^{43,44}

SURGICAL INTERVENTION

Early surgical therapy is generally reserved for patients with fulminant CDI. Approximately 3% to 10% of patients who acquire CDI progress to fulminant colitis.⁴⁵⁻⁴⁹ However, one of the more difficult challenges facing surgeons who care for CDI patients is deciding the most appropriate time to offer operative intervention. One would like to operate before the patient spirals too deeply into an unsalvageable physiologic state, but refrain from subjecting a patient who would otherwise recover with medical therapy to the morbidity of a surgical procedure.³³

Initial approaches to surgical intervention in patients with CDI utilized a variety of surgical options, including partial

colectomies and decompressive operations. These operations had a much higher mortality when compared with total abdominal colectomy with end ileostomy,^{10–13,26} making this latter procedure the primary surgical option for treatment of fulminant CDI.⁵⁰ However, this operative procedure is associated with appreciable morbidity and mortality in these critically ill patients.^{45,44} In various series, the mortality of patients undergoing surgery for CDI ranged from 35% to 80%.^{46–48}

Predictors of mortality in these patients included advanced age, lactic acidosis, thrombocytopenia, use of vasopressor or ventilatory support, perforation, toxic megacolon, increased Acute Physiology and Chronic Health Evaluation (APACHE II) and American Society of Anaesthesiologists (ASA) scores, and end-organ damage.^{48–51} However, these are also risk factors for mortality from the disease process itself, making the judgment to offer operative intervention difficult as it carries a high risk for complications and mortality, but could be a life-saving procedure.

Recently, a novel “intermediate” surgical option has been investigated. This procedure entails use of a minimally invasive technique to create a diverting loop ileostomy, through which direct colonic lavage with antibiotic solution is performed in the operating room and for several days in the postoperative period.⁵² Patient selection is the key. Patients should have appropriately severe disease (a diagnosis of CDI with one sign of physiologic compromise), but should not be in extremis. In the appropriate population, a 30% mortality reduction is reported with colonic preservation in greater than 90% of patients.⁵³ This colon-preserving surgical approach appears quite promising and may allow surgical intervention in patients with fulminant toxic colitis to be undertaken with less morbidity and mortality.⁵⁴ It may also paradoxically increase the utilization of surgical treatment for patients with severe CDI, as there may be less reluctance on the part of physicians and patients for an early surgical procedure if it does not lead to the morbidity of total colectomy.

Currently, there is no level I evidence to guide surgical decision making, due to limited data. Studies are limited by small sample size, retrospective design and lack of a consistent, established definition of fulminant CDI. The lack of data regarding opportune timing of surgical intervention, compounded by reported surgical mortality for CDI between 38% and 80%, results in a difficult decision-making process for the medical/surgical team, patient, and the patient's family.

As discussed previously, there is some data supporting the belief that earlier diagnosis and treatment is associated with mortality reduction. Additionally, outcome evaluation of emergency surgery for CDI reports indicators for increased postoperative mortality for patients in extremis (such as vasopressor-dependent shock, preoperative intubation, acute renal failure, and/or multisystem organ failure). Thus, we suggest surgical consult when medical therapy appears to be failing early in the patient's clinical course, allowing surgical monitoring in conjunction with the medical team, and potential early intervention based on the patient's condition.

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TOXICOLOGIC CONDITIONS

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Approach to Poisoning

Mohan Punja • Robert J. Hoffman

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INTRODUCTION

Patients with poison exposure and toxicity may present with a spectrum of various clinical signs, symptoms, and problems. Most of these are very straightforward and easily anticipated, but others may be unpredictable or associated with exposure to unidentified substances that hinder the clinician from knowing what to expect. There are, however, general principles that may be employed as a framework on which the approach to most poisonings may be based. These are employed when managing adverse effects from poisoning by known or unidentified substances. Less than 5% of poisonings require use of specific antidotes; thorough general supportive care is the most important approach in caring for most poisoned patients.¹

The initial principles of management of poisoned patients generally follow the protocol used for the management of urgent and emergent problems. There are some slight differences if the “airway, breathing, circulation” approach is used, with some specific amendments relevant to poison exposures and toxicity. “Airway, breathing, circulation, disability, dextrose, exposure, ECG” comprise the general “A, B, C, D, D, E, E” mantra of poison management. This may differ from other emergency department (ED) management in that “disability” and “exposure,” necessary for patients with trauma, are not essential in most poisoned patients, but can reveal some valuable diagnostic information.

HISTORY

Critical to proper management of poisoning is recognition that poison exposure occurred. When evaluating a poisoned

patient, a good approach is to identify the reason of exposure (intentional, unintentional, misadventure), the type of substance involved (prescription, over-the-counter, herbal, illicit drug), the formulation (immediate vs. sustained release), the dose of the substance, the amount of substance involved, the route of exposure (ingestion, inhalation, intravenous, dermal), the time of exposure (hours since exposure, acute vs. chronic), any potential coingestion, and the severity of exposure.

Obtaining a medical history from the poisoned patient may be difficult; therefore, other people such as family members, friends, prehospital personnel, the patient’s physician or therapist, or previous medical records may provide crucial information to aid in management. Thorough medical knowledge of all ailments, medical history, medication history, and other medications or substances that the patient had access to often provides useful information.

After initial assessment, stabilization, and physical exam, further management may include (1) decontamination, (2) prevention of absorption, (3) administration of antidote, and (4) enhanced elimination of the toxic substance.

PHYSICAL EXAMINATION

Examination of patients with poison exposure and toxicity is often more focused than a general physical examination, with particular attention to areas that are expected to yield useful information (Table 49-1).

Assessment of vital signs, neurologic status, pupils, skin, bowel, and bladder permits the recognition of a *toxidrome*. A toxidrome, or toxicologic syndrome, is a constellation of signs and symptoms that herald toxicity from a category of poisons. Recognition of the presence of a toxidrome is useful in



TABLE 49-1: Common Findings in Poisoning

Clinical and/or laboratory findings in poisoning

Agitation	Anticholinergics, ^a ethanol and sedative–hypnotic withdrawal, hypoglycemia, phencyclidine, sympathomimetics ^b
Alopecia	Alkylating agents, radiation, selenium, strontium, thallium
Ataxia	Benzodiazepines, carbamazepine, carbon monoxide, ethanol, hypoglycemia, lithium, mercury, phenytoin, nitrous oxide
Blindness or decreased visual acuity	Caustics (direct), cocaine, cisplatin, mercury, methanol, quinine, thallium
Blue skin	Amiodarone, FD&C #1 dye, methemoglobin, silver, sulfhemoglobin
Constipation	Anticholinergics, ^a botulism, lead, opioids, thallium (severe)
Tinnitus, deafness	Aminoglycosides, cisplatin, heavy metals, loop diuretics, quinine, salicylates
Diaphoresis	Amphetamines, cholinergics, ^c ethanol and sedative–hypnotic withdrawal, hypoglycemia, opioid withdrawal, salicylates, serotonin syndrome, sympathomimetics ^b
Diarrhea	Arsenic and other metals/metalloids, boric acid (blue-green), botanical irritants, cathartics, cholinergics, ^c colchicine, iron, lithium, opioid withdrawal, radiation
Dysesthesias, paresthesias	Acrylamide, arsenic, ciguatera, cocaine, colchicine, <i>n</i> -hexane, thallium
Gum discoloration	Arsenic, bismuth, hypervitaminosis A, lead, mercury
Hallucinations	Anticholinergics, ^a dopamine agonists, ergot alkaloids, ethanol, ethanol and sedative–hypnotic withdrawal, LSD, phencyclidine, sympathomimetics, ^b tryptamines (e.g., AMT)
Headache	Carbon monoxide, hypoglycemia, monoamine oxidase inhibitor/food interaction (hypertensive crisis), nitrites, serotonin syndrome
Metabolic acidosis (elevated anion gap)	Cyanide, ethylene glycol, ketoacidosis (diabetic, starvation, alcoholic), iron, isoniazid, lactic acidosis, metformin, methanol, paraldehyde, phenformin, protease inhibitors, salicylates, toluene, uremia
Miosis	Cholinergics, ^c clonidine, opioids, phencyclidine, phenothiazines
Mydriasis	Anticholinergics, ^a botulism, methanol, opioid withdrawal, sympathomimetics ^b
Nystagmus	Barbiturates, carbamazepine, carbon monoxide, ethanol, lithium, monoamine oxidase inhibitors, phencyclidine, phenytoin, quinine
Purpura	Anticoagulant rodenticides, clopidogrel, corticosteroids, heparin, pit viper venom, quinine, salicylates, warfarin
Radiopaque ingestions	Arsenic, “body packer,” chloral hydrate, enteric-coated tablets, halogenated hydrocarbons, metals (e.g., iron, lead)
Red skin	Anticholinergics, ^a boric acid, disulfiram interaction, hydroxocobalamin, scombroid, vancomycin
Rhabdomyolysis	Carbon monoxide, doxylamine, HMG CoA reductase inhibitors, sympathomimetics, ^b <i>Tricholoma</i> mushrooms
Salivation	Arsenic, caustics, cholinergics, ^c ketamine, mercury, phencyclidine, strychnine
Seizures	Bupropion, carbon monoxide, cyclic antidepressants, ethanol and sedative–hypnotic withdrawal, <i>Gyromitra</i> mushrooms, hypoglycemia, isoniazid, theophylline
Tremor	Antipsychotics, arsenic, carbon monoxide, cholinergics, ^c ethanol, lithium, mercury, methyl bromide, sympathomimetics, ^b thyroid replacement
Weakness	Botulism, diuretics, magnesium, neuromuscular blockers, paralytic shellfish, steroids, toluene
Yellow skin	Acetaminophen (late), <i>Amanita</i> mushrooms, β -carotene, dinitrophenol, pyrrolizidine alkaloids

^aAnticholinergics: for example, antihistamines, atropine, cyclic antidepressants, and scopolamine.

^bSympathomimetics: for example, amphetamines, β -adrenergic agonists, cocaine, ephedrine, and methylxanthines.

^cCholinergics: for example, muscarinic mushrooms, organic phosphorus compounds, and carbamates, including Alzheimer drugs and physostigmine, pilocarpine, and other direct-acting cholinergics.

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managing patients with exposure to unidentified substances and is also useful after known exposure to a category of substances known to cause a specific toxidrome (See Table 49-2).

Traditionally, there are four described toxidromes: adrenergic/sympathomimetic, anticholinergic, cholinergic, and opioid. There is also a well-recognized pattern of clinical findings associated with sedative–hypnotic substances. The classes of substances causing toxidromes include:

- **Adrenergic (sympathomimetic):** Sympathomimetic agents capable of α - and/or β -adrenergic agonism, for example, cocaine, amphetamines, theophylline, caffeine, pseudoephedrine, ephedrine, epinephrine, nor-epinephrine, and methylenedioxymethamphetamine (MDMA, known as Ecstasy).
- **Anticholinergic:** Substances that block cholinergic receptors, for example, atropine, scopolamine,

antihistamines, phenothiazines, cyclic antidepressants, and cyclobenzaprine.

- **Cholinergic:** Substances that afflict cholinergic receptors, for example, organophosphate pesticides and nerve agents, physostigmine, rivastigmine, and nicotine.
- **Opioid:** Substances that afflict opioid receptors, for example, heroin, morphine, hydromorphone, methadone, diphenoxylate, clonidine, and tramadol.
- **Sedative-hypnotic:** Substances that increase gamma-aminobutyric acid (GABA) activity, for example, benzodiazepines, barbiturates, alcohols, gamma-hydroxybutyrate (GHB), and zolpidem.

It is important to note that patients presenting with potential toxicity may have a mixed clinical picture and may not entirely fall under a specific toxidrome. This is particularly true for patients presenting with polydrug overdoses, or in cases in which an ingested drug has been adulterated with another toxidrome-causing substance.

DIAGNOSIS

The investigations and assays most useful in management of poisoned patients are commonplace in emergency medicine and critical care. Although it is possible to assay for hundreds of substances capable of causing toxicity, the most frequently indicated investigations are familiar to the ED and critical care physicians and are readily available in any setting in which emergency and critical care are delivered.

Electrocardiogram

Electrocardiograms (ECGs) are indicated in patients with exposure to substances capable of inducing dysrhythmia,

exposure to unidentified substances, and exposures with intent of self-harm. Most often, ECGs obtained in the ED setting for nonpoisoned patients are for the purpose of detecting ischemic changes. For patients with poison exposures and toxicity, evaluation for changes in cardiac conduction, conduction intervals, and dysrhythmia is of greatest interest. Ischemia is certainly of interest if present, but this is not the primary focus of ECG evaluation in patients with poison exposure and toxicity.

The triad of pseudo right bundle branch block—consisting of a tall R wave in AVR, S wave in lead I, and S wave in AVL—are highly sensitive indicators of sodium channel blockade resulting from tricyclic antidepressant exposure.² If these findings are present, prolongation of QRS duration to 100 ms and 160 ms is predictive of seizure and ventricular dysrhythmia, respectively.^{3,4} The finding of a terminal R-wave in lead AVR (defined by an amplitude of > 3 mm or a ratio of amplitudes between the R and S wave of > 0.7) has been suggested to be more useful than a QRS of greater than 100 ms for predicting seizure or arrhythmia.⁵

Dysrhythmias may result from toxins too numerous to list. Characteristic changes with ventricular bradydysrhythmia are seen with digoxin and other cardiac glycoside toxicity. Nonspecific ST changes throughout all leads, and occasionally bradycardia, accompany lithium toxicity.

Poison-induced dysrhythmias may require very different management from the same dysrhythmia that occurs due to other causes. In such cases, use of the “standard” management will be ineffective, and occasionally use of the standard management algorithm will increase morbidity and mortality. Some of these management techniques are described by the American Heart Association.⁶ Patients with poison-induced cardiac dysrhythmias should be managed by clinicians



TABLE 49-2: Common Findings in Toxidromes and Poisonings

Group	Vital Signs								
	BP	P	R	T	Mental Status	Pupil Size	Peristalsis	Diaphoresis	Other
Anticholinergics	−/↑	↑	±	↑	Delirium	↑	↓	↓	Dry mucous membranes, flush, urinary retention
Cholinergics	±	±	−/↑	−	Normal to depressed	±	↑	↑	Salivation, lacrimation, urination, diarrhea, bronchorrhea, fasciculations, paralysis
Ethanol or sedative-hypnotics	↓	↓	↓	↓	Depressed	±	↓	−	Hyporeflexia, ataxia
Opioids	↓	↓	↓	↓	Depressed	↓	↑	−	Hyporeflexia
Sympathomimetics	↑	↑	↑	↑	Agitated	↑	−/↑	↑	Tremor, seizures
Withdrawal from ethanol or sedative-hypnotics	↑	↑	↑	↑	Agitated, disoriented, hallucinations	↑	↑	↑	Tremor, seizures
Withdrawal from opioids	↑	↑	−	−	Normal, anxious	↑	↑	↑	Vomiting, rhinorrhea, piloerection, diarrhea, yawning

↑, increase; ↓, decrease; ±, variable; −, change unlikely; BP, blood pressure; P, pulse; R, respirations; T, temperature. (Reproduced with permission from Hoffman RS, Howland ME, Lewin NA, et al: *Goldfrank's Toxicological Emergencies*, 10th edition. New York: McGraw-Hill Companies Inc; 2014.)

familiar with, and preferably experienced with, these clinical scenarios. (See also Chapter 50: “The Critically Ill Poisoned Patient.”)

Laboratory—Routinely Indicated Assays

Serum glucose measurement and serum electrolyte analysis are the two most indicated lab assays in the management of poisoned patients. These tests allow detection of hypoglycemia, which may result from a variety of poisons, including both agents known to cause hypoglycemia and substances that may cause hyperglycemia and a subsequent hypoglycemic response. Any patient with altered mental status—including depressed or altered sensorium, coma, or agitation—should have immediate bedside assessment of the blood glucose level. This assay provides a result that is immediately interpretable, meaningful to the treating clinicians, and allows an anticipated, appropriate response with administration of dextrose or glucagon. Serum chemistry assessment allows detection of anion gap metabolic acidosis; alterations of sodium, potassium, and serum bicarbonate; and alterations of the other measured substances.

The anion gap is calculated by the following formula: $[\text{Na}^+] - [\text{Cl}^- + \text{HCO}_3^-]$, and the normal value is generally accepted to be between 6 and 14 mEq/L.⁷ Discovery of an elevated anion gap in the poisoned patient should prompt investigation of the cause, if unknown. Such causes may be exogenous or endogenous etiologies as represented by the MUDPILES mnemonic: methanol, uremia, diabetic ketoacidosis, paraldehyde/phenformin, iron/inhalants (carbon monoxide, cyanide, and hydrogen sulfide), isoniazid/ibuprofen, lactic acidosis, ethylene glycol/ethanol ketoacidosis, and salicylates/solvents (benzene, toluene)/sympathomimetics/starvation ketoacidosis.

Measurement of the serum osmolar gap is occasionally useful in the patient with suspected toxic alcohol ingestion, but has many limitations. The measured serum osmolality is compared with the calculated serum osmolality to derive the gap that represents other osmotically active substances. The formula is $\text{Osm}_{\text{calc}} = 2[\text{Na}^+] + (\text{BUN}/2.8) + (\text{glucose}/18) + (\text{ethanol}/4.6)$. Methanol, ethylene glycol, and numerous other drugs, chemicals, and disease states may contribute to this gap. There is a wide, poorly defined range of “normal” osmolar gap, usually ranging from -5 to $+15$ mOsm/kg.^{8,9} Given that the patients’ baseline osmolar gap is rarely known, it is difficult to reliably determine if an unmeasured osmotically active substance is present. Thus, the change in this gap as the toxic alcohol is metabolized, in conjunction with the anion gap and any laboratory levels of alcohols, is more important; a “normal” osmolar gap does not rule out exposure to a toxic alcohol.

Additional laboratory assays that are commonly useful include serum acetaminophen level, salicylate level, ethanol level, and blood gas analysis. Serum acetaminophen assays are indicated for any patient with potentially toxic exposure to acetaminophen and any patient with exposure with intent of self-harm, regardless of whether acetaminophen expo-

sure is reported,¹⁰ and may be useful in patients with elevation of hepatic transaminases after exposure to unidentified substances.

Serum salicylate levels may aid in detection of undisclosed salicylate exposure. Salicylate toxicity may be identified by clinical findings,¹¹ but these may be obscured by polydrug exposure, other medical ailments, or lack of clinician exposure to salicylate-poisoned patients.¹² We advocate routine use of serum salicylate screening in patients with unidentified exposures or exposures with intent of self-harm.

Serum ethanol levels may provide insight into causality of depressed mental status. Although wide variability in patient tolerance to ethanol makes interpretation of serum ethanol level and correlation with degree of depression of consciousness less than fully accurate,¹³ this assay is a staple of ED assessment of patients with depressed consciousness.

Readers are advised to interpret serum ethanol level with caution. Overlooking other emergent causes of depressed or altered mental status—such as intracranial hemorrhage, encephalitis, or sepsis—by inappropriately attributing the mental state to ethanol exposure is a very common error in emergency medicine. This error routinely results in morbidity and mortality, and is a common cause for legal cases brought against treating physicians. The presence of a serum ethanol level capable of causing intoxication should not cause the clinician to discontinue investigating potential emergent causes of altered or depressed mental status.

Blood gas analysis is useful for a variety of reasons, including to elucidate the type and degree of acidosis or alkalosis, detect dyshemoglobinemias through carboxyhemoglobin or methemoglobin level, and determine oxygen extraction and utilization in poisonings that may result in blockade of oxidative phosphorylation, such as by cyanide. In nearly all cases, with the most common exception of cardiac arrest, venous blood gas sampling has been shown to be nearly equivalent to arterial sampling for the assessment of pH and pCO_2 . The simplest correction or correlation of pH between venous and arterial blood gas samples is performed by adding 0.03 to the venous pH to obtain the arterial pH.^{14,15} In most cases, venous blood gas sampling is adequate,^{14,15} and arterial blood sampling should be performed only when necessary. An exception to this general rule is evaluation for cyanide or other disruptors of oxidative phosphorylation, in which comparison of simultaneously obtained arterial and venous blood gas samples is used to assess oxygen extraction across the capillary and tissue bed.

Serum creatine phosphokinase may be obtained when a patient exhibits signs of altered temperature regulation and muscle tone, such as in the serotonin and neuroleptic malignant syndromes or the sympathomimetic toxidrome. Additionally, many common drugs have the potential to cause rhabdomyolysis, the most well known of which are statins, steroids, theophylline, and doxylamine. Any condition that has the potential to cause trauma or prolonged immobilization, such as the abuse of rapid-onset sedatives, may damage muscle, thereby releasing potentially dangerous amounts of potassium and creatine phosphokinase.

Laboratory—Quantitative Assays

Generally, on exposure to a substance for which a serum concentration, or “level,” may be obtained, such information may potentially be highly useful for management and/or prognosis. Occasionally, these are critical to selecting a specific management, especially hemodialysis, other method of enhanced elimination, or antidote administration.

Laboratory—Drug of Abuse Screening

Laboratory screening for drugs of abuse,—commonly, amphetamines, cannabinoids (marijuana), cocaine, PCP, and opioids—is the toxicology lab screening that is least useful, most overutilized, and most misunderstood and misinterpreted toxicologic lab assay.^{16,17} Other than for forensic purposes, lab assay for drugs of abuse is not routinely indicated for patients with exposure to drugs of abuse or for patients with unidentified exposures. As these screenings are only qualitative, they confirm only that exposure to the substance in question that occurred within the previous days or week, depending on the substance. Many such assays are not complete for the respective drug category. A screening assay specific for amphetamine might not detect methamphetamine or MDMA (Ecstasy), which are much more widely abused than amphetamine. A typical opioid screening will detect natural opioids but not synthetic opioids, such as methadone, fentanyl, propoxyphene, tramadol, and so on. Many commonly abused drugs, such as ketamine and GHB, are not detected by any routine laboratory screening. With the explosion of designer drugs such as synthetic cannabinoids and “bath salts” (phenylethylamine derivatives), the potential pitfall of the urine assay for drugs of abuse is even greater. In addition, many medications known to cause false-positive drug-of-abuse screening exist. The tricyclic antidepressant screening assay is notorious for false positives, as there are many medications that possess a similar three-ringed structure. Screening for cocaine is the most accurate of the commonly used drug-of-abuse screening tests, but the tested metabolite benzoylecgonine typically is detectable in urine for only 2 to 3 days after a single exposure.

Failure to understand the limitations of drug-of-abuse screening leads uninformed clinicians to obtain this test, and often to misinterpret the results.

Malicious exposures, exposures in children incapable of voluntarily using drugs, and other circumstances for which forensic evidence of drug abuse exposure would be useful should be obtained in consultation with physicians with forensic experience and law enforcement officials. It is important to remember that the urine lab assay for drugs of abuse is a screening test; thus, positive findings should be confirmed by a confirmatory test, which is typically gas chromatography-mass spectrometry. This is particularly true of forensic samples.

Additionally, psychiatric consultants commonly utilize the results of drug-of-abuse screening to determine treatment protocols for patients with substance abuse in the setting



FIGURE 49-1 Iron tablet overdose. The identification of the large amount of radiopaque tablets corroborates the diagnosis in a patient with a suspected iron overdose. (Used with permission from Toxicology Fellowship of the New York City Poison Center.)

of psychiatric disease after the acute phase of an overdose is managed.

Imaging

Occasionally, imaging may be useful in evaluation. Some radiodense materials—such as lead, heavy metals, enteric-coated tablets, and ingested packages containing drugs such as cocaine or heroin—may be identified by plain radiography. In some circumstances, abdominal X-ray may reveal radiopaque materials, such as hydrocarbons, that may cause a characteristic “double bubble” sign in the stomach. Two heavy metals particularly amenable to detection by plain films are nonchewable iron tablets and ingested lead containing foreign bodies. The sensitivity of plain X-ray to identify ingested drug packages, used for trafficking drugs of abuse, is very high. Classic findings may include visualization of staples used to hold packs closed, “rosettelike finding” of air trapped in knots where packets are tied, and the “double condom” sign in which air is seen trapped between layers of latex (Figures 49-1 and 49-2).¹⁸

Computerized tomography (CT) may also be indicated to identify ingested substances such as ingested drug packages or radiodense materials. In the case of rupture of ingested packages, CT scanning should be performed after surgery to document complete gastrointestinal (GI) tract clearance.¹⁸

Imaging is also useful to evaluate for the consequences of poisoning. Examples are chest radiograph, which may identify pneumonitis associated with hydrocarbon or other aspiration; abdominal radiograph, showing bowel obstruction or perforation; or CT, which may provide information about the extent and severity of injury from caustic ingestion.

Endoscopy may provide direct imaging of the airway or GI tract and may be particularly useful in patients with caustic exposures to aid in diagnosis, discharge, and prognosis. We recommend endoscopy with all intentional caustic ingestions and most nonalkali exposures. In children, stridor, or the combination of drooling and vomiting, should prompt



FIGURE 49-2 A patient in police custody was brought to the emergency department for allegedly ingesting drug packets. The patient admitted swallowing several plastic bags that were stapled closed. (Used with permission from Toxicology Fellowship of the New York City Poison Center.)

endoscopy.¹⁹ When indicated, endoscopy should be performed within 8 to 12 hours and no later than 24 hours.

DECONTAMINATION, PREVENTING DRUG ABSORPTION, AND ENHANCED ELIMINATION

Decontamination to prevent adverse effects of poison exposure has long been advocated as a poison management strategy. The concept that removing a poison from the body may avert illness is easily understood by laypersons and clinicians alike, and this strategy seems to make common sense. Despite this, repeated and rigorous testing of GI decontamination methods has routinely failed to demonstrate any convincing benefit. GI decontamination plays an increasingly small and marginal role in the management of poisoned patients. External decontamination of the skin and eyes continues to play a vital role in some poison management.

External and Ocular Decontamination

When a toxin is on a patient's body, external decontamination should be performed to protect staff from becoming ill and to limit ongoing toxicity to the patient. This is best performed at a designated shower or mass casualty decontamination area near the entrance of the ED. The patient should

be completely disrobed; jewelry, watch, and so on, should be removed and the entire body or exposed area thoroughly washed. For ocular exposures, the eyes are irrigated with copious isotonic solution (such as normal saline or lactated Ringer's) for at least 30 minutes or until a normal ocular pH is obtained. For full efficacy, a Morgan lens should be used in the affected eye, and ocular anesthetic such as tetracaine or proparacaine should be instilled prior to the procedure.²⁰

GI Decontamination

Multiple methods of GI decontamination are available to reduce the bioavailability of an ingested toxin. Most of these methods are outdated and provide little clinical benefit; however, there may be scenarios appropriate for their use.

Emesis induced by syrup of ipecac is not recommended for routine use,²¹ and we recommend against its use except in the specific scenario of the alert, conscious patient within an hour of a large ingestion of a potentially fatal toxin (not a corrosive substance or hydrocarbon) that is not adsorbed to activated charcoal (AC). The emesis induced by ipecac is unpredictable in duration, and may limit more useful methods of decontamination. GI lavage is the passage of a large-bore orogastric tube to administer liquid and aspirate a toxic substance in the stomach. Due to serious risks and limited benefit, there is no place for the routine use of lavage, but use in the critically ill patient with toxic ingestion, depressed mental status, and instability presenting within 1 hour of ingestion may be appropriate.^{22,23} Multiple studies of gastric lavage strategies in volunteer patients have shown the most efficacy when performed within 30 minutes, with diminishing results as time progresses up to 1 hour and minimal benefit after 1 hour.

Use of nasogastric lavage to aspirate liquid poisons does not carry the same degree of risk of orogastric lavage and has been demonstrated to reduce poison absorbed.²² Nasogastric aspiration of liquid poison may be performed in patients presenting after ingestion of liquid poison who are still anticipated to have poison remaining in the stomach. The small size of the typical nasogastric tube limits its utility for removing pill fragments.

Whole bowel irrigation (WBI) is a method of emptying the GI tract in order to limit further absorption of a toxin. This is typically done using a warmed polyethylene glycol–electrolyte solution (PEG–ES) at rates of 0.5 to 1 L/h in adults, which often requires the placement of a nasogastric or orogastric tube.²⁴ WBI may be performed in select situations, for example, large and potentially fatal ingestions of substances not bound by charcoal such as iron or lead, sustained-release preparations, or in the body packing of illicit substances. It is contraindicated in bowel obstruction, ileus, perforation, GI hemorrhage, hemodynamic instability, unstable airway, or potential for deterioration of the airway.²⁴

Of all methods of GI decontamination, AC has the most potential benefit but is still not recommended for routine use in the poisoned patient.²⁵ AC may be used at 1 g/kg up to 100 g, and is best performed within 1 hour of ingestion, with limitations similar to WBI. It decreases the bioavailability of


TABLE 49-3: Selected Normal and Toxic Lab Values for Common Substances, and Potential Actions to be Taken

Substance	Therapeutic or Normal Level	Toxic or Actionable Level	Action
Acetaminophen	10–30 µg/mL	> 150 µg/mL or if toxic on Rumack–Matthew nomogram	<i>N</i> -acetylcysteine
Caffeine	1–10 µg/mL	> 25 µg/mL chronic > 90 µg/mL acute	Multiple-dose activated charcoal Dialysis
Carboxyhemoglobin	0–2% up to 10% in smokers	> 15% (dependent on patient symptoms/pregnancy)	Oxygen + hyperbaric oxygen chamber
Cyanide	< 1 µg/mL		Cyanide antidote kit
Digoxin	0.8–2.0 ng/mL	> 2.0 ng/L	DigiFab
Ethylene glycol	0 mg/dL	> 25 mg/dL	Fomepizole and/or dialysis
Iron	80–180 µg/dL	> 500 µg/dL	Deferoxamine
Lead	< 10 µg/dL	> 25 µg/dL	Deferoxamine, calcium EDTA, dimercaprol, or succimer
Lithium	0.6–1.2 mEq/L	> 2.5 mEq/L chronic > 4.0 mEq/L acute	Hemodialysis
Methanol	0 mg/dL	> 25 mg/dL	Fomepizole and/or hemodialysis
Methemoglobin	< 1%	> 15–20%	Methylene blue
Phenobarbital	15–40 mg/L	> 100 µg/mL	Hemoperfusion exchange transfusion in infants
Phenytoin	10–20 mg/L	> 30 mg/L	Multidose activated charcoal
Salicylates	15–30 mg/dL	> 30 mg/dL chronic > 60 mg/dL acute	Urine alkalinization Hemodialysis
Theophylline	5–15 µg/mL	> 25 µg/mL chronic > 90 µg/mL acute	Multidose activated charcoal Hemoperfusion/dialysis

a wide variety of toxins but is not useful for the ingestions of alcohols, corrosives (acids/alkalis), magnesium, potassium, or metals such as iron and lithium. A majority of the adverse effects related to AC are from aspiration or direct administration of charcoal into the lungs.²⁶ Oral administration of AC is contraindicated in a patient with a significantly altered mental status or an inability to protect the airway. Endotracheal intubation done in conjunction with gastric decontamination such as gastric lavage or administration of WBI or AC lessens, but does not completely eliminate, the risk for aspiration.

Enhanced Elimination

Enhancing elimination of a toxin is indicated in patients who have decreased elimination of a drug (i.e., renal failure with ingestion of drug that is mainly eliminated in the urine) or in toxins that have a prolonged elimination half-life. Multidose AC may be used in the appropriately alert patient with potential severe toxic or fatal ingestions of carbamazepine, dapsone, phenobarbital, quinine, phenytoin, and theophylline, or in cases of ingestion of long-acting or enteric formulations, and in bezoar formation.²⁷ After the initial dose of AC, administer 0.25 to 0.5 g/kg Q 2 to 6 hours for up to 12 hours.

Urine alkalinization is a method of enhancing elimination of weakly acidic toxins by trapping them in an alkaline urine compartment. This is recommended only as first-line

treatment of moderately severe salicylate poisoning and as second-line treatment in the ingestion of fluoride, methotrexate, phenobarbital, 2,4-dichlorophenoxyacetic acid, and mecoprop.²⁸ For phenobarbital, multidose AC alone seems to be more effective than urinary alkalinization or the combination of the two therapies. A urine pH of 8.0 can be achieved by an initial bolus of 1 to 2 ampules of sodium bicarbonate followed by an infusion of two to three ampules in 1 L of D5W at 1.5 times maintenance with concurrent aggressive repletion of potassium.

Hemodialysis and charcoal hemoperfusion are the most invasive and expensive methods of enhancing elimination of toxins and have the added advantage of improving acid–base and electrolyte imbalances. Salicylate, methanol, ethylene glycol, theophylline, caffeine, carbamazepine, lithium, and procainamide (refer to Table 49-3) are amenable to dialysis.

Antidotes

Although most management of the poisoned patient is supportive care, the judicious use of an antidote is sometimes the only therapy capable to prevent morbidity or mortality. Examples of this are the administration of hydroxocobalamin or sodium thiosulfate for cyanide poisoning; oxygen for carbon monoxide toxicity; digoxin Fab for digoxin toxicity; fomepizole and/or ethanol for toxic alcohol poisoning; *N*-acetylcysteine

for acetaminophen toxicity; and calcium for calcium channel blocker overdose. Specific antidotal therapies are discussed in more detail in the following chapters, including newer therapies for critically ill poisoned patients such as hyperinsulinemia-euglycemia therapy and lipid emulsion therapy.

Critically ill patients who present with symptoms justifying reasonable suspicion for poison exposure can also be treated empirically. Examples of this include empirical use of naloxone in patients with respiratory depression and pinpoint pupils or use of pyridoxine for the child in status epilepticus whose household member is being treated for tuberculosis with isoniazid.

Antivenin exists for the hematologic, neurologic, and cytotoxic effects of the two main categories of snakes in the United States (Elapidae and Crotalinae). There are other antivenins for scorpions and spiders that are available in specific geographic areas of the United States where they are relevant. There are also antivenins for rare, nonindigenous exotic snakes that are imported and used in zoos and research facilities and occasionally used to treat envenomation from exotic animals illicitly imported and kept as pets. These exotic antivenins tend to be available at facilities that must be prepared for such envenomations, such as zoos or the hospitals that serve them.

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The Critically Ill Poisoned Patient

Robert J. Hoffman

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INTRODUCTION

The 2001 publication by the American Heart Association, *TOX-ACLS Toxicologic-Oriented Advanced Life Support*,¹ marked wide recognition that critical illness resulting from poisoning may require very different management from similar illness occurring in the nonpoisoned patient. That publication made specific suggestions for management of dysrhythmias and other toxicity caused by cocaine, calcium channel blockers and β -blockers, opioids, tricyclic antidepressants, and drug-induced cardiovascular shock. In 2010, the updated American Heart Association ACLS guidelines contained specific evaluation and recommendations regarding poisoning with these same aforementioned toxins, as well as cyanide, digoxin, and antidotal therapy with flumazenil and lipid emulsion.² The relevance of those publications is recognition that proper management of many clinical problems caused by toxins differs or deviates from management of the same clinical problem occurring in the nonpoisoned patient.

The main focus of this chapter is on the most commonly encountered critical problems in the clinical management of poisoned patients. We present a general approach to management and discuss the unique management issues involving poisoning. This chapter cannot cover all poisoning circumstances that require unique management, but it does cover the most common problems relevant to intensivists.

Although the severe consequences of poisoning and toxicity may cause a wide array of clinical problems, the majority of critical illnesses resulting from poisoning involve the following problems: (1) airway or respiratory compromise; (2) cardiovascular depression manifested as hypotension and/or bradycardia; (3) cardiovascular stimulation manifested as hypertension,

tachycardia, and/or tachydysrhythmia; (4) hyperthermia; and (5) seizure and status epilepticus (Table 50-1).

COMPROMISED AIRWAY AND RESPIRATION

As with other clinical circumstances, airway management is nearly universally the primary concern in management of the poisoned patient. Airway compromise, respiratory depression, and/or respiratory compromise must be immediately addressed, and, when possible, their underlying etiology corrected or addressed.

Endotracheal Intubation and Unique Considerations

The decision to perform endotracheal intubation in the poisoned patient is based on expectation of lack of continuing airway patency and concerning prognostic factors. Although Glasgow Coma Score (GCS) was not developed to be used as a guide to airway and respiratory status, in many poisonings it can predict the need for endotracheal intubation and/or mechanical ventilation. Patients with a GCS of ≤ 6 as a result of poisoning often require endotracheal intubation.³

There are numerous exceptions to the principle of GCS < 6 being predictive of need for intubation, including toxicity from dissociative agents that cause depressed mental status or coma but do not typically compromise airway and respiration.⁴ Such agents include ketamine, phencyclidine (PCP), and dextromethorphan; agents that cause waxing and waning respiratory compromise, primarily clonidine; γ -hydroxybutyrate



TABLE 50-1: Unique Management of Selected Toxins and Associated Illnesses

Toxin	Effect	Pathophysiology	Unique Therapy
Multiple toxins	Toxin-induced seizure	Multiple pathways	Use benzodiazepines, barbiturates, empirical pyridoxine, or propofol. Do not administer phenytoin
Carbon monoxide	Metabolic acidemia, cardiovascular depression, dysrhythmia, seizure, cardiac arrest	Binds hemoglobin and myoglobin preventing oxygen delivery, binds cytochrome oxidase	Oxygen therapy, hyperbaric oxygen therapy
Caustic exposure	Airway compromise due to burn	Direct tissue injury and inflammation	Emergently secure a definitive airway by endotracheal intubation
Clonidine	Apnea, respiratory depression, cardiovascular depression	Opioidlike effect	Physical stimulation of patient when apneic High-dose naloxone infusion
Cyanide	Metabolic acidemia, cardiovascular depression, dysrhythmia, seizure, cardiac arrest	Blocks oxidative phosphorylation	Antidotal use of hydroxocobalamin or cyanide antidote kit (nitrites and sodium thiosulfate)
Methemoglobinemia	Metabolic acidemia, cardiovascular depression, dysrhythmia, seizure, cardiac arrest	Alters hemoglobin, preventing oxygen delivery	Methylene blue
Organophosphate	Apnea, bronchorrhea, bronchospasm, cardiovascular depression	Muscarinic cholinergic agonism	Prolonged paralysis may result from neuromuscular blockade due to diminished pseudocholinesterase
Organophosphates	Cholinergic syndrome, bradycardia, bronchorrhea, bronchospasm, cardiovascular depression, dysrhythmia, seizure, cardiac arrest	Inhibits acetylcholinesterase, cholinergic excess	Decontamination outside of clinical care area supersedes A, B, C and resuscitation Allowing contaminated patient into clinical treatment area risks ongoing patient toxicity and potential poisoning of staff caring for patient
Salicylate	Hyperventilation	Centrally mediated and compensatory to metabolic acidemia	Even brief interruption of hyperventilation may result in rapid or immediate death. Initial respiratory rate and volume initially 150% of normal
Stimulants, hallucinogens	Cardiovascular stimulation; hyperthermia secondary to psychomotor agitation		Use benzodiazepines for agitation, cardiovascular stimulation
Theophylline, caffeine	Cardiovascular depression, dysrhythmia	β -Adrenergic agonism, adenosine antagonism	Short-acting β -blocker administration to treat refractory hypotension
Tricyclic antidepressants	Cardiovascular depression, dysrhythmia	Multiple effects	Use of direct-acting pressors Use of sodium bicarbonate to reduce sodium channel blockade

(GHB) and its congeners may also fit into this category. This latter group may result in apnea and/or respiratory depression that is reversible with stimulation of the patient.

An exceptional circumstance warranting rapid securing of the airway is airway compromise secondary to caustic exposure. Due to the potential for rapid deterioration and loss of ability to secure an airway later, it is advisable to endotracheally intubate patients with caustic exposure and stridor, aphonia, or dysphonia in a manner similar to that conducted for an airway burn.⁵

Certain toxins require specific considerations when performing endotracheal intubation. Poisoning with organophosphate pesticides deactivates pseudocholinesterase,

resulting in an extremely prolonged half-life of paralytic agents used for neuromuscular blockade.⁶ This should be taken into consideration when administering these medications and when selecting agents based on their half-life and duration of action.

Salicylate toxicity results in metabolic acidemia with respiratory alkalemia due to salicylate stimulation of central respiratory drive and compensatory increase in respiratory drive.⁷ In salicylate-poisoned patients, increased minute ventilation is achieved through tachypnea and/or hyperpnea. Interrupting this for even the brief time required to perform endotracheal intubation may result in rapid or immediate seizure or cardiovascular collapse.⁸ Endotracheal intubation in a patient

with salicylate toxicity should be undertaken only when necessary and performed by a clinician with the highest capability to complete the procedure rapidly. Immediately after endotracheal intubation, the patient should be ventilated at 150% of both the rate and volume typically used. Serial blood gas analysis will allow rate and volume settings to be adjusted. Failure to maintain hyperventilation may result in rapid or immediate death.

A unique exception to the “airway, breathing, circulation” paradigm familiar to emergency medicine and critical care clinicians is physical decontamination of patients. Allowing a contaminated patient to enter clinical areas without proper decontamination is a well-documented risk to caregivers and other patients and is capable of rendering an emergency department’s critical care unit incapable of providing effective care. Even the presence of patients with detectable odors due to minimally toxic substances has well-recognized potential to be disruptive and generate unease and panic, causing vague, nonspecific but incapacitating symptoms in a manner best described as hysteria.⁹ Accordingly, any patient contaminated with highly toxic substances capable of cross-contaminating staff or clinical areas, such as organophosphate pesticides and certain hydrocarbons, absolutely must be decontaminated in a “hot” or “warm” zone outside the “cool” zone in which only decontaminated patients are managed and in which clinical care is provided. It is an appropriate practice for a contaminated patient to be kept outside the emergency department, even if unstable, apneic, or in a state of cardiovascular collapse, until decontamination is accomplished.

When securing the airway in a setting with clinicians wearing personal protective equipment, consider use of a laryngeal mask airway (LMA) rather than endotracheal intubation, as LMA placement is less impacted by wearing cumbersome PPE suits.¹⁰

Poisons Affecting Respiratory Drive and Ventilation

Numerous drugs and medications may cause hypoventilation by blunting central respiratory drive, most notably sedative–hypnotic medications such as benzodiazepines, barbiturates, and alcohol, and opioids such as morphine, heroin, and fentanyl.

In addition to central blunting of respiratory drive, hypoventilation may occur as a result of impaired chest wall movement. This may be due to weakness or paralysis, as occurs from exposure to botulinum toxin, pesticides and other organophosphates, and neuromuscular blockers, or from hypokalemia and hypermagnesemia. Chest wall rigidity can cause hypoventilation, and may result from tetanus, strychnine, or fentanyl exposure. For fentanyl chest wall rigidity, also termed “wooden chest,” use of naloxone in standard or high doses may be attempted. Chest wall rigidity from tetanus or strychnine may be relieved with neuromuscular blockers (Table 50-2).

By far the most common effect, if any, toxins will have on respiratory status is to induce respiratory depression.



TABLE 50-2: Drugs and Medications Causing Hypoventilation

Baclofen	γ-Hydroxybutyrate and analogs
Barbiturates	Isopropanol
Botulinum toxin	Methanol
Carbamates	Neuromuscular blockers
Clonidine	Nicotine
<i>Conium maculatum</i> (Poison Hemlock)	Opioids
Colchicine	Organic phosphorous compounds
Cyclic antidepressants	Sedative–hypnotics
Elapid envenomation	Strychnine
Electrolyte abnormalities	Tetanus toxin
Ethanol	Tetrodotoxin
Ethylene glycol	

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Certain unique toxins, however, result in increase in central respiratory drive. Caffeine and theophylline, which are used therapeutically to increase respiratory drive in neonatal apnea syndrome,¹¹ salicylates, and cocaine result in increased respiratory rate by stimulation of central respiratory drive. Salicylates additionally have metabolic effects that cause peripheral effects that additionally increase respiratory drive.

Poisons Affecting Cellular Respiration

Certain poisons affect respiration on the cellular or molecular level. This may commonly result from alteration of hemoglobin to form methemoglobin or carboxyhemoglobin, both of which are incapable of normal oxygen delivery. Cellular or molecular impairment of respiration may also occur by interference with oxidative phosphorylation, such as by poisoning with cyanide, carbon monoxide, or hydrogen sulfide.

METHEMOGLOBIN

Methemoglobinemia results from oxidative stress on hemoglobin that results in iron oxidation to the ferric (Fe^{3+}) rather than standard ferrous (Fe^{2+}) state.¹² This derivative of hemoglobin binds H_2O rather than oxygen, and does not deliver oxygen to tissues. Methemoglobinemia presents clinically with expected results of hypoxia: tachypnea, dyspnea, and severe cyanosis. Pulse oximetry readings in this condition are inaccurate due to inability of standard pulse oximeters to interpret methemoglobin light absorption because standard pulse oximeters are only intended to quantify oxyhemoglobin and deoxyhemoglobin. Methemoglobinemia typically results in pulse oximetry readings that range from 75% to 85% on standard pulse oximeters. Co-oximeters are capable of precisely measuring oxyhemoglobin, deoxyhemoglobin, methemoglobin, and carboxyhemoglobin, and can accurately quantify the precise methemoglobin level.¹³ They are laboratory devices that interpret blood gas samples, not to

be confused with pulse oximeters, which are bedside devices that estimate hemoglobin saturation using light absorption. Normal methemoglobin levels are 0.5–3%. Methemoglobin levels > 10% may be associated with symptomatic illness, and levels > 50% may result in rapid death. Treatment of methemoglobinemia involves administration of high-flow oxygen and chemical reduction of the methemoglobin back to hemoglobin using methylene blue.

In the normal state, small quantities of methemoglobin may be converted back to hemoglobin through an NADH-dependent reaction catalyzed by cytochrome *b₅* reductase. This is the mechanism by which nontoxic quantities of methemoglobin that form during day-to-day exposure to oxidants correct methemoglobinemia. During severe methemoglobinemia, this reaction is insufficient, and an alternative metabolic pathway that does not function without the aid of an exogenously administered reducing agent is needed. The reducing agent used therapeutically is methylene blue, and it works by acting through the hexose monophosphate shunt to reduce methemoglobin, yielding normal, functional hemoglobin.

Optimal methylene blue dosing is unknown, and numerous varied recommended doses exist. Methylene blue may result in hemolysis in G6PD-deficient persons and should be avoided or used with extreme caution in them. Dosing of methylene blue is 1–2 mg/kg given IV over 5 minutes.¹⁴ Response is usually very rapid, but if methemoglobin levels remain elevated 1 hour later, methylene blue may be readministered at the same dose. Methylene blue interferes with pulse oximetry reading, and continued use of co-oximetry by measurement of venous blood gas samples is required to monitor methemoglobin levels. Dapsone toxicity may cause prolonged methemoglobinemia due to the long half-life of dapsone. Repeated treatments with methylene blue, not to exceed 5 mg/kg/24 hours, may be required in symptomatic patients.

CARBON MONOXIDE

Carbon monoxide is a by-product of combustion. Carbon monoxide poisoning typically results from closed-space fires or by exposure to exhaust from combustion engines. Carbon monoxide binds hemoglobin with an affinity approximately 250 times greater than that of oxygen.¹⁵ Carbon monoxide binding of hemoglobin results in carboxyhemoglobin, which is a nonfunctional form of hemoglobin that does not transport oxygen. Carbon monoxide binding of myoglobin creates additional hypoxemic stress by further decreasing the ability of muscle tissue to use oxygen. This is of particular concern because it can contribute to myocardial ischemia.

Clinical problems resulting from acute carbon monoxide poisoning include headache, nausea, vomiting, disorientation, altered mental status or coma, syncope, seizure, and cardiac arrest. Chronic carbon monoxide poisoning presents differently, often with headache and malaise that may be misdiagnosed as a viral syndrome.

Carboxyhemoglobin is not detected by standard bedside pulse oximetry. Pulse oximeters misinterpret carboxyhemoglobin as oxyhemoglobin and therefore give a falsely normal

pulse oximetry reading in patients with carbon monoxide poisoning. Co-oximetry measurement of carboxyhemoglobin level in venous or arterial blood gas is required to quantify degree of carbon monoxide binding of hemoglobin. There is no “normal” carboxyhemoglobin level, but average persons have levels < 3% that may result from exposure to automobile exhaust and other sources. Smokers have notably higher carbon monoxide levels¹⁶ based on how heavily they smoke, and they may have baseline carboxyhemoglobin levels as high as 10%.

Symptomatic illness from carbon monoxide poisoning may occur acutely with any level of carboxyhemoglobin, but is typical at levels > 10%. Depending on the health of the patient, severe illness and injury may occur with carboxyhemoglobin levels as low as 10%, although healthy individuals usually tolerate higher levels. Significant acute carbon monoxide poisoning results from levels > 25%, and levels > 45% are immediately life-threatening.¹⁷

Treatment of carbon monoxide toxicity involves administering supplemental oxygen. This may be normobaric or, if possible, hyperbaric oxygen. Hyperbaric oxygen does not have notable immediate benefit to the patient, but is administered to prevent the potentially devastating neurologic sequelae of poisoning.¹⁸ These sequelae include a Parkinson-like syndrome and extreme neuropsychiatric disability that may render the patient incapable to work, study, or pursue the usual activities of daily living.

CYANIDE

Cyanide toxicity results from cyanide binding to cytochrome *a₃*, which interferes with oxidative phosphorylation. This prevents cellular respiration, in effect suffocating the tissues on a cellular level. Cyanide exposure may result from inhalation of smoke in closed-space fires.^{19,20} Fires have been recognized to often produce copious quantities of cyanide that result from burning of plastic, polyurethane, rubber, silk, wool, and many other materials typically contained in homes and offices. Cyanide poisoning may result iatrogenically from prolonged use of nitroprusside, which contains cyanide and the antiquated antineoplastic agent laetrile. Certain plants, such as pits or seed from peaches, apricots, plums, pears, apples, and bitter almond, are cyanogenic. Cyanide is used commonly in the jewelry industry and in some fields such as photography. Homicidal and suicidal use of cyanide is well reported.

Cyanide toxicity presents clinically with acute onset of severe illness after exposure. This is typically syncope, coma, seizure, cardiac dysrhythmia, or cardiac arrest. Due to inability to use oxygen in oxidative phosphorylation, fair-skinned patients typically have a flushed, pink appearance. Lab corroboration of cyanide toxicity may be obtained by comparing arterial and venous blood gas samples drawn simultaneously and by noting a lack of oxygen extraction across the capillary bed.²¹ Metabolic acidemia is always present and usually severe. In the setting of closed-space fires, lactate concentration > 10 mmol/L is pathognomonic for cyanide toxicity.¹⁹ This appears to be true regardless of the presence of carbon monoxide poisoning or the extent of body surface burn.¹⁹

Serum cyanide levels are rarely clinically available but are of use if they can be obtained rapidly. Cyanide levels < 1.0 mg/L correlate with tachycardia and flushing; 1.0–2.5 mg/L with altered mental status, seizure, and hypotension; and levels > 3.0 mg/L are typically rapidly fatal.

Treatment for cyanide toxicity involves use of hydroxocobalamin, which is the optimal antidote, or use of all or part of the cyanide antidote kit, which is a combination of amyl nitrite pearls, sodium nitrite, and sodium thiosulfate.^{22,23}

Cyanide antidote therapy should be given to any patient with known or suspected exposure to cyanide or from a closed-space fire if he or she has metabolic acidemia, elevation of lactate concentration, loss of consciousness or altered mental status, shock, cardiac dysrhythmia, or cardiac arrest. Due to the recognition that closed-space fires may result in cyanide poisoning, an increasing number of prehospital systems, such as New York City, have protocols for ambulance crews to administer hydroxycobalamin in the field in appropriate circumstances.²⁴ This is highly appropriate, since other therapies such as supplemental oxygen, IV fluids, and even CPR do not address the underlying problem and will ultimately fail if a cyanide antidote is not administered.

Hydroxocobalamin, a vitamin B₁₂ precursor, directly binds cyanide to form vitamin B₁₂, which is harmless and excreted in the urine. If available, hydroxycobalamin is preferable to the traditional cyanide antidote kit. Some experts recommend using hydroxycobalamin and the thiosulfate portion of the cyanide antidote kit. Because hydroxycobalamin and sodium thiosulfate work by different mechanisms, have no pharmacologic interactions, and are each very safe, combination treatment with hydroxycobalamin and sodium thiosulfate is considered optimal for cyanide poisoning.²⁵

Dosing of hydroxocobalamin is 70 mg/kg, to a maximum dose of 5 g, given IV over 30 minutes. In cases of cardiac arrest, it can be given as an IV push. The dose can be repeated to a maximum total of 15 g. Use of hydroxocobalamin may subsequently interfere with pulse oximetry readings and co-oximetry readings, rendering it difficult or impossible to know oxygen saturation, leaving only measurements of Po₂ as a guide.²⁶ These interferences may last as long as several days.

Use of the cyanide antidote kit involves three parts: amyl nitrite inhalation pearls, sodium nitrite for IV administration, and sodium thiosulfate for IV administration. Nitrates are used to induce methemoglobinemia. These are only used in cyanide toxicity not resulting from closed-space fires and smoke inhalation. After closed-space fire, carbon monoxide poisoning may concomitantly be present, and a decrease in oxygen-carrying capacity by causing formation of methemoglobin is contraindicated. For patients who possibly have carbon monoxide poisoning, only the sodium thiosulfate portion of the kit is administered.²² This works by enhancing formation of cyanomethemoglobin through the enzyme rhodanese.

Use of the various portions of the kit are as follows: amyl nitrite pearl is crushed and inhaled for 1 minute until IV access is obtained. The sodium nitrite dose is 10 mL of the 3% solution included in the kit; pediatric dosing is

0.33 mL/kg. Hypotension may result from nitrite use. Nitrites are intended to cause methemoglobinemia; if a methemoglobin level of > 10–15% is not induced by the initial dosing of sodium nitrite, half of the original dose may be administered 30–60 minutes after the first dose.

Sodium thiosulfate is administered as 12.5 g IV, which is the full 50-mL bottle of 25% sodium thiosulfate solution included in the kit. The pediatric dose is 1.65 mL/kg of the same 25% solution. Repeat dosing of sodium thiosulfate may be given as one half of the original dose 30–60 minutes after the initial dose.

CARDIOVASCULAR DEPRESSION

Cardiovascular depression in the form of hypotension and/or bradycardia may result from exposure to cardioselective medications, such as digoxin, β -adrenergic antagonists, calcium channel antagonists, and clonidine, and also occurs from numerous other toxins. As a preterminal event, cardiovascular depression may result secondary to toxicity from any poison, including cardiovascular stimulants. Treatment of cardiovascular depression from certain toxins, particularly cardioselective medications, may require very specific, unique therapy.

Asymptomatic hypotension and/or bradycardia, particularly in the absence of end-organ manifestations, do not necessarily indicate treatment. The lower limit at which clinicians are comfortable allowing heart rate or blood pressure to remain varies. Generally, maintaining the heart rate at 45 beats/min or greater, systolic blood pressure > 90 mm Hg, and diastolic blood pressure > 40 mm Hg, or mean arterial pressure > 65 mm Hg are limits above which vital signs should be maintained.

Intravenous fluid bolus, atropine, and pressors may be used to treat cardiovascular depression with exceptions noted here. Bradycardia resulting from most cardioactive medications infrequently responds to atropine because homeostatic mechanisms will have already decreased or removed vagal tone in an attempt to compensate. Use of atropine is not contraindicated for medications such as digoxin, β -adrenergic antagonists, calcium channel antagonists, and clonidine, but more effective and definitive therapy should not be delayed due to atropine administration.

Pressors similarly may lack their typical effectiveness when used in poisoned patients. As with all patients, care should be exercised in balancing attempts to maintain central arterial or venous pressure with end-organ or extremity capillary perfusion pressure to prevent paradoxical hypoperfusion of organs, digits, and extremities with high-dose pressor infusions (Tables 50-3 and 50-4).

Tricyclic Antidepressant Hypotension

If an indirect or mixed-acting pressor is used without success, particularly in cases of hypotension from tricyclic antidepressants, norepinephrine should be initiated. The pathophysiology of cyclic antidepressant poisoning may result in

 **TABLE 50-3: Drugs and Medications Causing Bradycardia**

α_1 -Adrenergic agonists (reflex bradycardia)
Phenylephrine
Phenylpropanolamine
α_2 -Adrenergic agonists (centrally acting)
Clonidine
Methyldopa
β -Adrenergic antagonists
Antidysrhythmics
Amiodarone
Sotalol
Calcium channel blockers
Cardioactive steroids
Cholinergics
Carbamates or organic phosphorous compounds
Edrophonium
Neostigmine
Physostigmine
Opioids
Sedative–hypnotics
Sodium channel openers
Aconitine
Andromedotoxin
Ciguatoxin
Veratridine

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catecholamine depletion to a degree that no quantity of an indirect-acting agent such as dopamine will be effective, and norepinephrine or epinephrine may be necessary.

Digoxin Cardiovascular Depression

Specific unique therapies for cardioactive medication toxicity may be indicated. Cardiotoxicity from digoxin, digitoxin, or other cardioactive steroids such as bufotoxin may be treated with digoxin-specific Fab.²⁷ Although this antidote is produced for digoxin, cross-specificity with digitoxin, bufotoxin from toad species, oleandrin from oleander, and other botanical cardiac glycosides typically respond to digoxin-specific Fab. Empirical dosing for acute digoxin toxicity is 10–15 vials in adults or children. In cases of oleander, toad, or other related poisoning, the typical dose for acute digoxin toxicity may be used, and additional doses may be needed.

β -Blocker Cardiovascular Depression

β -Blocker toxicity typically does not respond significantly to IV fluid, atropine, or pressors. Glucagon is often effective, since its activity is independent and unaffected by blockade of the β -adrenergic receptors.²⁸ An empirical dose of glucagon is 5 mg SC or IV in adults, 1 mg in children < 20 kg, or 2 mg in children > 20 kg. If effective, glucagon may be administered again as necessary. If glucagon therapy proves to be ineffective, more than two consecutive attempts to restore cardiovascular function should not be attempted using this therapy.

 **TABLE 50-4: Heart Rate and ECG Abnormalities of Drugs Causing Hypotension**

Heart Rate	Characterstics ECG Abnormalities		
	Sinus Rhythm	Heart Block or Prolonged Intervals	Dysrhythmia
Bradycardia	α_2 -Adrenergic agonists Opioids Sedative–hypnotics	β -Adrenergic antagonists Calcium channel blockers Cholinergics Cardioactive steroids Magnesium (severe) Methadone Propafenone Sotalol	Digoxin Plant toxins Aconitine Andromedotoxin Veratrine Propafenone Propoxyphene Sotalol
Tachycardia	Angiotensin-converting enzyme inhibitors Anticholinergics Arterial dilators Bupropion Cocaine Disulfiram Diuretics Iron Yohimbine	Anticholinergics Antidysrhythmics Antihistamines Arsenics Bupropion Cocaine Cyclic antidepressants Phenothiazines Quinine/chloroquine	Anticholinergics Antidysrhythmics Antihistamines Arsenics Chloral hydrate Cocaine Cyclic antidepressants Methylxanthines Noncyclic antidepressants Phenothiazines Sympathomimetics

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Calcium Channel Blocker Cardiovascular Depression

Calcium channel antagonists are unique cardiotoxins. Due to calcium channel blockade, patients with calcium channel antagonist overdose often maintain normal mentation even in the state of extremely low systolic and mean arterial blood pressure. This phenomenon is so characteristic and notable that normal mental status in the presence of extreme hypotension/bradycardia should be considered highly suggestive of calcium channel antagonist toxicity.

Therapy for calcium channel antagonists includes administration of high-dose calcium. Calcium gluconate or calcium glubionate is effective, and its concentration is safe to be used in peripheral veins. Calcium chloride contains three times the elemental calcium of calcium gluconate and therefore has some advantage in use. Extreme caution must be exercised to avoid extravasation of calcium chloride. An antidotal therapy used regularly for the past decade that is highly effective in treating calcium channel antagonist-induced cardiovascular depression is insulin–euglycemia.²⁹

Pathophysiologically, the healthy myocardium uses free fatty acids for energy. Myocardium that is unhealthy, stressed, or in a shock state will utilize glucose for energy, and it is believed that this is the mechanism by which insulin–glucose infusion aids calcium channel blocker–induced cardiovascular depression.

Hyperinsulinemia/Euglycemia Therapy

Insulin–euglycemia therapy involves initiating a 1 U/kg bolus of regular insulin with 0.5 g/kg of dextrose. If the blood glucose is > 400 mg/dL prior to the insulin bolus, no glucose bolus is necessary. After the initial bolus, an insulin infusion of 0.5–1.0 U/kg/h with a continuous dextrose infusion beginning at 0.5 g/kg/h should be started. This dextrose is best infused at D25 or D50 given by central venous access to limit free water administration. The dextrose infusion may be titrated to give more or less dextrose as needed to maintain acceptable serum glucose.

Cardiac function should be reassessed every 20–30 minutes. In cases of persistent cardiovascular depression, the insulin infusion may be increased in increments of 0.5 U/kg/h every 30 minutes if needed to a maximum dose of 2.5 U/kg/h. Increasing the insulin infusion dose will require an increase in the amount of dextrose infused.

The initial response to insulin–euglycemia therapy is typically not seen immediately, and it may take 20–40 minutes after initiation of therapy to detect clinical response in cases in which the therapy is successful.

It is critical to monitor the blood glucose frequently during this therapy, every 30 minutes at minimum until stable, and then every 1 hour after the insulin infusion, glucose infusion, and blood glucose are stable. It is also necessary to monitor the serum potassium, since some degree of hypokalemia is expected. Stable hypokalemia at levels down to 2.5 mEq/L does not require supplemental potassium administration but will require close monitoring.

Lipid Emulsion Therapy

Lipid emulsion therapy may be used in treatment of lipophilic cardiotoxins of all types: calcium channel blocker, β -blocker, local anesthetic, tricyclic antidepressants, and others.³⁰ Lipid emulsion is administered as an initial bolus of intralipid or other lipid emulsion in a 20% concentration in a 1.5 mL/kg followed by 0.25 mL/kg/min or 15 mL/kg/h to run for 30 or 60 minutes. Occasionally, a prolonged infusion in a dose of 1–2 g/kg per day or 5–10 mL/kg per day is necessary. Although propofol contains lipid, it should never be used as the agent to provide the lipid for this antidotal therapy. The quantity of propofol to lipid is such that an extremely toxic overdose of propofol would be necessary to deliver an adequate dose of lipid for lipid emulsion therapy.

Clonidine Cardiovascular Depression

Clonidine is an α -agonist with opioidlike effects, and toxicity often mimics the opioid toxidrome of miosis, coma, and apnea.³¹ In known or suspected clonidine toxicity, high-dose naloxone may be used if the patient is not opioid tolerant. Opioid-tolerant patients are expected to have severe opioid withdrawal as a result of naloxone administration. This may result in severe vomiting and aspiration if depressed mental status is present. If high-dose naloxone is effective at improving respiratory effort or cardiovascular depression resulting from clonidine, an infusion of two-thirds of the dose that achieved clinical response given hourly is recommended. This may be titrated as needed.

Caffeine and Theophylline Hypotension

Hypotension from theophylline or caffeine results from excess β -stimulation, including β_2 , which causes hypotension. This hypotension may involve a characteristically widened pulse pressure, in which the difference between systolic and diastolic pressures may be 150% or greater than the diastolic pressure. Therapy of hypotension resulting from severe theophylline or caffeine toxicity is best carried out by typical use of IV fluid and pressors. If this is unsuccessful, administration of a short-acting β -adrenergic antagonist, such as esmolol, may be highly effective in reducing or eliminating hypotension.³² Blockade of β_2 agonism in such cases may result in rapid and complete resolution of hypotension as well as typical metabolic effects of theophylline toxicity such as hyperglycemia and hypokalemia.³¹ Esmolol is preferred due to a titratable effect; long-acting β -blockers are not recommended.

CARDIOVASCULAR STIMULATION

Cardiovascular stimulation in the form of hypertension, tachycardia, and/or tachydysrhythmia commonly results from a variety of poisonings. Cocaine toxicity is the most commonly encountered situation and requires unique therapeutic approach to control cardiovascular stimulation.

Cocaine causes release of large quantities of catecholamines in a dose-dependent manner. Therefore, the primary pharmacologic treatment of cocaine toxicity, including cardiovascular stimulation and cocaine chest pain, is benzodiazepines, often required in very large doses. Benzodiazepines counteract this effect and typically result in abatement of hypertension and tachycardia, as well as psychomotor agitation.

If liberal administration of benzodiazepines fails to decrease BP associated with cocaine or other stimulant use, use of anti-hypertensives may be required. During the initial years of the introduction of crack cocaine into the United States, numerous case reports followed by large case series documented a paradoxical rise in blood pressure in cocaine-intoxicated patients treated with β -blockers. Some of these resulted in catastrophic or fatal intracranial hemorrhage and other sequelae of severe hypertension. The mechanism by which β -blockers may cause increased rather than decreased blood pressure in cocaine-intoxicated patients is by removal of β -adrenergic tone, leaving unopposed α -adrenergic tone and extreme vasoconstriction. For this reason, β -blockers should generally be avoided in management of cocaine-induced cardiovascular stimulation. If benzodiazepine therapy is inadequate to control cardiovascular stimulation, use of phentolamine is preferred to treat hypertension. Other therapies may include use of nitrites, such as nitroglycerine or nitroprusside, and calcium channel blockers, including both conduction-modulating agents such as verapamil and diltiazem, or dihydropyridines such as nifedipine, nicardipine, and others.

Some centers do not adhere to the admonishment to avoid β -blocker use. In such settings, labetalol is often used because it has some degree of α - as well as β -blockade. Use of other β -blockers should only follow or accompany concomitant use of an α -blocking agent such as phentolamine.

Sympathetic nervous system stimulation by cholinergic poisons such as pesticides is a less commonly encountered situation requiring unique care. Acetylcholine excess may cause muscarinic excess, secondary bradycardia/hypotension, or nicotinic excess with secondary stimulation of the sympathetic chain ganglia and tachycardia/hypertension. It may also cause alternation between cardiovascular stimulation and depression. For this reason, management of cardiovascular stimulation secondary to cholinergic poisons such as organophosphates should be managed by use of short-acting, titratable medications such as esmolol or nitroprusside. Such use allows rapid cessation of the medication if the patient transitions from a state of cardiovascular stimulation to cardiovascular depression (Table 50-5).

HYPERTHERMIA

Pathophysiologically, there are several ways in which poison exposure and toxicity may result in hyperthermia. By alteration of normal mental state, cognition, and psychomotor agitation, patients may be unaware of own temperatures or that of their surroundings. They may fail to avoid exercise or activity in hot ambient environments, become unable to leave the environment, or continue to exert themselves



TABLE 50-5: Drugs and Medications Causing Hypertension

Hypertensive Effects Mediated by α -Adrenergic Receptor Interaction	Hypertensive Effects Not Mediated by α -Adrenergic Receptor Interaction
Direct α -receptor agonists	β -Adrenergic receptor agonists ^a
Clonidine ^b	Nonselective
Epinephrine	Isoproterenol
Ergotamines	Cholinergics ^b
Methoxamine	Corticosteroids
Norepinephrine	Nicotine ^b
Phenylephrine	Thromboxane A ₂
Tetrahydrozoline	Vasopressin
Indirect-acting agonists	
Amphetamines	
Cocaine	
Dexfenfluramine	
Monoamine oxidase inhibitors	
Phencyclidine	
Yohimbine	
Direct- and indirect-acting agonists	
Dopamine	
Ephedrine	
Metaraminol	
Naphazoline	
Oxymetazoline	
Phenylpropanolamine	
Pseudoephedrine	

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^aThese can also cause hypotension.

^bThese may cause transient hypertension followed by hypotension.

while restrained. Examples include becoming comatose in a closed automobile during daytime or on a hot surface such as asphalt, where heat gain by conduction may occur quickly. Commonly, this may occur with drugs of abuse such as ethanol, cocaine, opioids, and PCP. Psychomotor agitation associated with drugs of abuse may also result in significant heat production.

Such cases are understandably more common in warmer months. A clear relationship between deaths from cocaine hyperthermia and ambient temperature exists. Deaths from cocaine hyperthermia in New York City, for example, dramatically peak during the warmest summer months and are rare during other times.³³ This is likely true for other drugs that cause psychomotor agitation and hyperthermia, as well.

Other pathophysiologic mechanisms for hyperthermia include uncoupling of oxidative phosphorylation, such as with salicylate or dinitrophenol toxicity; increased metabolism, such as from thyroid hormone or thyroid extract toxicity; impaired sweating, such as from antihistamines and anticholinergics; and vasoconstriction due to α -adrenergic agonism, such as from amphetamines, cocaine, pseudoephedrine, and

other sympathomimetics. Malignant hyperthermia (MH), resulting from ryanodine receptor dysfunction, as well as serotonin syndrome (SS) and neuroleptic malignant syndrome (NMS), is discussed later in this chapter.

Although differing pathophysiology underlies the manner in which hyperthermia is reached, the initial acute treatments are similar. The temperature at which permanent neurologic injury will occur in any patient cannot be known, but a core temperature of 107°F or 42°C warrants active cooling, preferably by immersion in ice or an ice bath. Tepid sponging, mist spray and fans, or other less effective measures should only be used in the instance when true ice immersion cannot be achieved.

A simple method of ice immersion is placing the patient in a partially closed body bag enclosed with ice. Covering the patient in ice and wrapping in a sheet or blanket is also suitable, understanding that this will quickly result in water pooling on the floor surrounding the patient as the ice melts. If a cholera bed is available, this aids in collection of melting ice water and is preferable from a nursing and housekeeping perspective. Using immersion makes cardiopulmonary monitoring more difficult.

Typically, patients with hyperthermia resulting from psychomotor agitation, hypermetabolism, or uncoupled oxidative phosphorylation do not feel uncomfortable in an ice pack or ice bath. After some period of time when the temperature decreases, they may communicate that they feel cold or uncomfortable, and this often correlates with reaching a goal temperature of 100–102°F. Care should be taken to carefully monitor patients to avoid overcooling below normal body temperature.

Treatment of psychomotor agitation should include chemical restraint by benzodiazepine administration. Use of haloperidol is contraindicated for this purpose as it lowers seizure threshold, results in increased incidence of cardiac dysrhythmia, and impairs heat dissipation. In cases of true

MH, dantrolene is indicated. Dantrolene is often errantly used for hyperthermia from causes other than MH, in which there is no potential benefit and thus the small risk of use is not justified. Use of traditional antipyretics such as aspirin, acetaminophen, ibuprofen, ketorolac, naproxen, or others plays no role whatsoever in toxin-induced hyperthermia.

Hyperthermic Syndromes: Serotonin Syndrome, Neuroleptic Malignant Syndrome, and Malignant Hyperthermia

SS, NMS, and MH are unique toxin-induced illnesses that result in hyperthermia by different mechanisms (Table 50-6). These syndromes have significant overlap in clinical presentation, but careful evaluation can clearly differentiate between them. Hotline numbers for the Neuroleptic Malignant Syndrome Information Service are 1-888-667-8367 and 1-315-464-4001. Another hotline to aid in management of MH is the Malignant Hyperthermia Association of the United States, which can be reached at 1-800-644-9737 or 1-315-434-7079. These services are intended to provide advice about diagnosis and management of NMS and MH, respectively. They are supported by medical toxicologists and are able to assist in differentiating NMS, MH, and SS, and to make treatment recommendations.

Onset of illness and progression of illness are distinct for SS, NMS, and MH. SS develops over hours and universally < 24 hours after exposure to the serotonin agonist. SS is rapidly progressive and can quickly transition from mild illness to critical instability or death in hours. This helps differentiate from NMS, which develops over days, and for which both the progression and resolution occur over a more prolonged time period. MH develops more acutely than both SS and NMS, within minutes to hours, and nearly universally within 12 hours of exposure to the causal medication(s). It may



TABLE 50-6: Comparison of Findings in Serotonin Syndrome, Neuroleptic Malignant Syndrome, and Malignant Hyperthermia

Illness	Onset	Mental Status	Muscular Changes	Vital Signs	Offending Agent(s)	Treatment
Serotonin syndrome	Hours	Confused, agitated	Twitching, fasciculation, shivering, hyperreflexia	Severe hyperthermia, hypertension, tachycardia, hypotension, and bradycardia when deteriorating	Serotonergic medications and drugs of abuse	Cyproheptadine, active cooling
Neuroleptic malignant syndrome	Days	Catatonic, mute	Catatonic, lead-pipe rigidity	Mild hyperthermia < 102.5°F	Neuroleptic antipsychotic agents, withdrawal of anti-Parkinson dopamine agonists	Bromocriptine
Malignant hyperthermia	Minutes to hours	Poorly defined, patient usually sedated or anesthetized	Rigidity, may not be present if already paralyzed	Elevated EtCO ₂ Severe hyperthermia	Inhalational anesthetics, succinylcholine	Dantrolene, active cooling

rapidly progress and rapidly dissipate. As a result, initial diagnosis and treatment of MH infrequently involves emergency medicine or critical care physicians, usually occurs in operating rooms or postoperative recovery rooms, and is overseen by anesthesiologists managing the patient at that time.

SEROTONIN SYNDROME

SS results from excess serotonergic agonism, typically as a result of exposure to two or more serotonin agonists or massive exposure to a single serotonin agonist. The incidence of SS is increasing, both as a result of increase in prescription of serotonergic medications, as well as the increasingly widespread use of potent serotonergic drugs of abuse such as MDMA (Molly, Ecstasy) and similar related amphetamine analogues.

SS characteristically causes mental status changes, autonomic hyperactivity, and neuromuscular abnormalities. Alteration of mental status usually does not involve coma or impaired consciousness. Typically, it presents with anxiety, disorientation, psychomotor agitation, and hyperalertness, with patients startling easily. The neuromuscular findings may be hyperreflexia, clonus, tremor, muscle rigidity, myoclonus, hyperreflexia, and a unique form of shivering that is sometimes rhythmic and progressive along the torso, similar to that of a dog shaking water from its coat. Autonomic manifestations are tachycardia and hypertension, with hyperthermia.

To fulfill Hunter criteria to diagnose SS, the patient must have been exposed to a serotonergic medication or drug and have any of the following: (1) spontaneous clonus, (2) inducible clonus plus agitation or diaphoresis, (3) ocular clonus plus agitation or diaphoresis, (4) tremor and hyperreflexia, (5) hypertonia, and (6) temperature $> 38^{\circ}\text{C}$ plus ocular clonus or inducible clonus.

Laboratory abnormalities include myoglobinuria, elevated creatine phosphokinase (CPK), and hyperkalemia. In suspected cases, obtain blood gas analysis with lactate concentration, serum electrolytes, liver function tests, and CBC.

Treatment of SS includes maintaining vital signs within acceptable limits, including cooling to $< 39^{\circ}\text{C}$ (102.2°F), and use of benzodiazepines, as well as possibly cyproheptadine. Benzodiazepines treat agitation, serve as muscle relaxants, and are useful because the CNS side effects of benzodiazepines do not overlap with CNS changes that result from SS. Lorazepam 0.05–0.1 mg/kg IV is given every 20–30 minutes until clinical effect is reached, followed by repeat administration at the appropriate dose in 2- to 6-hour periods. Diazepam 0.1–0.5 mg/kg may also be used, with initial doses repeated every 10–15 minutes and repeat dosing every 1–2 hours as needed. If benzodiazepines fail to sedate thoroughly, cyproheptadine is given empirically in adults as a 12-mg initial dose followed by 2 mg every 2 hours until symptoms resolve. Dosing would be modified on a weight basis in children.

Cyproheptadine is only available in a PO formulation but can be crushed and administered down a nasogastric tube to patients with altered mental status. Medications such as chlorpromazine and olanzapine should not be used since they lower seizure threshold and increase risk of developing NMS.

NEUROLEPTIC MALIGNANT SYNDROME

NMS is an extrapyramidal syndrome associated with hyperthermia, muscle rigidity, autonomic instability, and altered mental status. This occurs predominantly with use of antipsychotics and less commonly when anti-Parkinson dopamine agonists are withdrawn.

NMS occurs in particular with potent antipsychotics such as haloperidol and fluphenazine and with depot formulations such as long-acting depot haloperidol injection, but it has been reported to occur from all classes of neuroleptic drugs, as well as new atypical antipsychotic agents.

Epidemiologically, NMS occurs more commonly in males and in younger patients, but can occur in any gender or age patient. NMS is an idiosyncratic reaction, meaning it is not dose dependent. It may occur with the first dose of medication or may occur in a patient who has been receiving the medication for years without any adverse side effects. NMS occurs more frequently within the first 2 weeks of initiating a neuroleptic or antipsychotic treatment, with depot injection use, and with rapid dose escalation. The pathophysiology and etiology of NMS are unknown but are widely believed to be mediated by central dopamine antagonism.

As mentioned, NMS may be differentiated from SS by timing of onset. NMS symptoms typically develop over several days, whereas SS develops over hours. Because NMS occurs in patients with psychiatric illness and is slower in onset, there is more likely to be delayed or missed diagnosis. Hyperthermia, altered mental status, autonomic instability, and muscle rigidity are universally present in patients with NMS.

Hyperthermia is usually not as extreme as with SS or MH, with temperatures typically in the range of $38\text{--}39^{\circ}\text{C}$ ($100.4\text{--}102.2^{\circ}\text{F}$) and uncommonly $> 40^{\circ}\text{C}$ (104°F). Muscular rigidity with NMS is more catatonic, lead-pipe rigidity, whereas SS is associated with fasciculation, twitching, shivering, and hyperreflexia. Mental status changes are also more similar to those of catatonic states, and patients may be mute, stuporous, or comatose.

Lab testing is critical in management of NMS, and, due to the slower time course of the illness, there is adequate time for lab testing. Elevations of CPK may be severe. Rhabdomyolysis and myoglobinuric renal failure may result. Expectedly, associated electrolyte abnormalities may include hyperkalemia and mild elevations of lactate. Low serum iron concentration has $> 95\%$ sensitivity in detecting NMS.³⁴

Management of NMS includes immediate discontinuation of the offending drug and supportive care with correction of dehydration and electrolyte imbalance. Cooling to decrease temperature to acceptable range may be carried out by the physical methods mentioned earlier in this section. Pharmacologic treatment for NMS should be administered. Hyperthermia from NMS is usually less severe than SS and typically will not require the aggressive measures to lower temperature that are commonly needed for SS.

Pharmacologic therapy for NMS includes bromocriptine, which agonizes dopamine receptors. This is only available as a PO formulation and may be crushed and given by nasogastric tube. Dosing is 2.5 mg PO Q 6–8 hourly. It is recommended

to continue this for 10–14 days after the symptoms of NMS have resolved. Amantadine may be used instead of bromocriptine. Benzodiazepines may also be used for muscle relaxation and to relieve psychomotor agitation. Lorazepam 2 mg IV/PO Q 6 h is typically effective, but this dose may be increased as necessary.

NMS resolution typically takes days to weeks, on average 5–15 days, to resolve. This is in contrast to SS, for which onset and resolution are often within hours.

MALIGNANT HYPERTHERMIA

MH is a hypermetabolic crisis typically encountered in the setting of anesthesia administration, and it may be seen in genetically susceptible patients who receive inhalational anesthetics and/or succinylcholine. As previously mentioned, MH is rarely encountered in the emergency department or ICU setting, and is typically managed in the operative and postoperative setting. Because MH is a toxin-induced hyperthermic crisis that develops within minutes to hours and is most likely to result in severe morbidity or mortality, clinicians who administer succinylcholine or manage postoperative patients should be aware of this entity and its management.

MH involves excessive release of calcium from the sarcoplasmic reticulum of myocytes and an ensuing hypermetabolism that results in hypercarbia, mixed respiratory and metabolic acidosis, rhabdomyolysis, and hyperthermia that is sometimes severe, with temperatures rapidly rising up to 113°F. It is widely misunderstood and misstated that hyperthermia rapidly develops in patients with MH: in fact, hyperthermia and rhabdomyolysis may be the last of the clinical symptoms to become apparent, occurring after muscle rigidity, hypercarbia, and mixed respiratory and metabolic acidemia.

The earliest clinical indication of MH is often hypercarbia. There is no absolute P_{CO_2} that is diagnostic, but a $P_{aCO_2} > 60$ –65 or end-tidal $CO_2 > 55$ –60 in the absence of other obvious cause should be considered suggestive in postoperative patients. This hypercapnia may be managed by increasing minute ventilation, although the increases required by mechanical ventilation are often greater than would normally be expected. If the patient is not already being mechanically ventilated, he or she should have airway support by endotracheal intubation or laryngeal mask airway and then be mechanically ventilated with 100% FiO_2 , with a minute ventilation that corrects the P_{CO_2} as reasonably as possible.

It is appropriate to correct hypercarbia, but investigation for other evidence of MH should be initiated. This includes physical exam to detect increased muscle tone; evaluation of arterial blood gas; urinary myoglobin, serum CPK, and serum potassium that may be associated with rhabdomyolysis; PT/PTT, INR, and fibrin split products to detect disseminated intravascular coagulation; and rectal or core temperature monitoring. Although hyperthermia is often not present when MH is initially suspected, when elevation of temperature does begin, it may be rapid, with temperatures rising as much as 2°F every 5 minutes.

At any time when MH is strongly suspected, any possible inciting medications should be discontinued and dantrolene administration should begin. Despite any other supportive care given, without dantrolene patients are extremely unlikely to survive MH.³⁵ Prior to the development of dantrolene, 70% of cases of MH were fatal. With current supportive care and dantrolene administration in the United States, approximately 10% of cases are fatal.

Supportive care includes correcting hypercarbia, providing 100% oxygen to support the hypermetabolic state, correcting hyperkalemia, treating rhabdomyolysis, managing disseminated intravascular coagulation if it occurs, and managing hyperthermia.

Use of active cooling as described in the beginning of this section is recommended in conjunction with dantrolene administration.

TOXIN-INDUCED SEIZURE

Seizure may be the consequence of numerous pathophysiologic events, most commonly metabolic and neurochemical. Management of seizure or status epilepticus resulting from poisoning varies significantly from management of epilepsy or trauma-associated seizure.³⁶ The initial management of toxin-induced seizures should include rapid bedside assessment of blood glucose and assessment for hypoxia.

Management of toxin-induced seizures differs from epileptic or traumatic seizures in that phenytoin use is contraindicated.³⁵ Specifically, phenytoin results in increases in severe seizure activity and increased incidence of cardiac dysrhythmia and death. Although the sodium channel blocking activity of phenytoin is effective in decreasing activity of epileptogenic foci or focal activity of traumatized brain, toxin-induced seizure activity is the culmination of diffuse and global cerebral dysfunction, for which sodium channel blockade both is unhelpful and may worsen seizure activity. It is ill-advised to treat toxin-induced seizure with phenytoin, as doing so is expected to be ineffective and, more importantly, to increase morbidity and mortality.

A management protocol for toxin-induced seizures can be summarized as follows: administration of a benzodiazepine, such as lorazepam 0.05–0.1 mg/kg every 10–15 minutes or diazepam 0.1–0.2 mg/kg every 5–10 minutes to a maximum of three doses. Further dosing is not detrimental, but use of benzodiazepines should be considered inadequate if three doses have not successfully terminated seizures, and escalation to more intensive therapy is warranted.

Benzodiazepine use should be followed by empirical dosing of pyridoxine (vitamin B₆) to treat the potential effect of isoniazid or other hydralazine-induced seizure if the offending drug is isoniazid or unknown. Dosing is 1 g pyridoxine for every 1 g of isoniazid or other hydrazine ingested. Empirical dosing is 2–4 g in adults or 70 mg/kg in children. Because pyridoxine is not often immediately accessible at the dose required, this may be ordered from the pharmacy and progression down the treatment algorithm continues, with pyridoxine administered as soon as it is available.

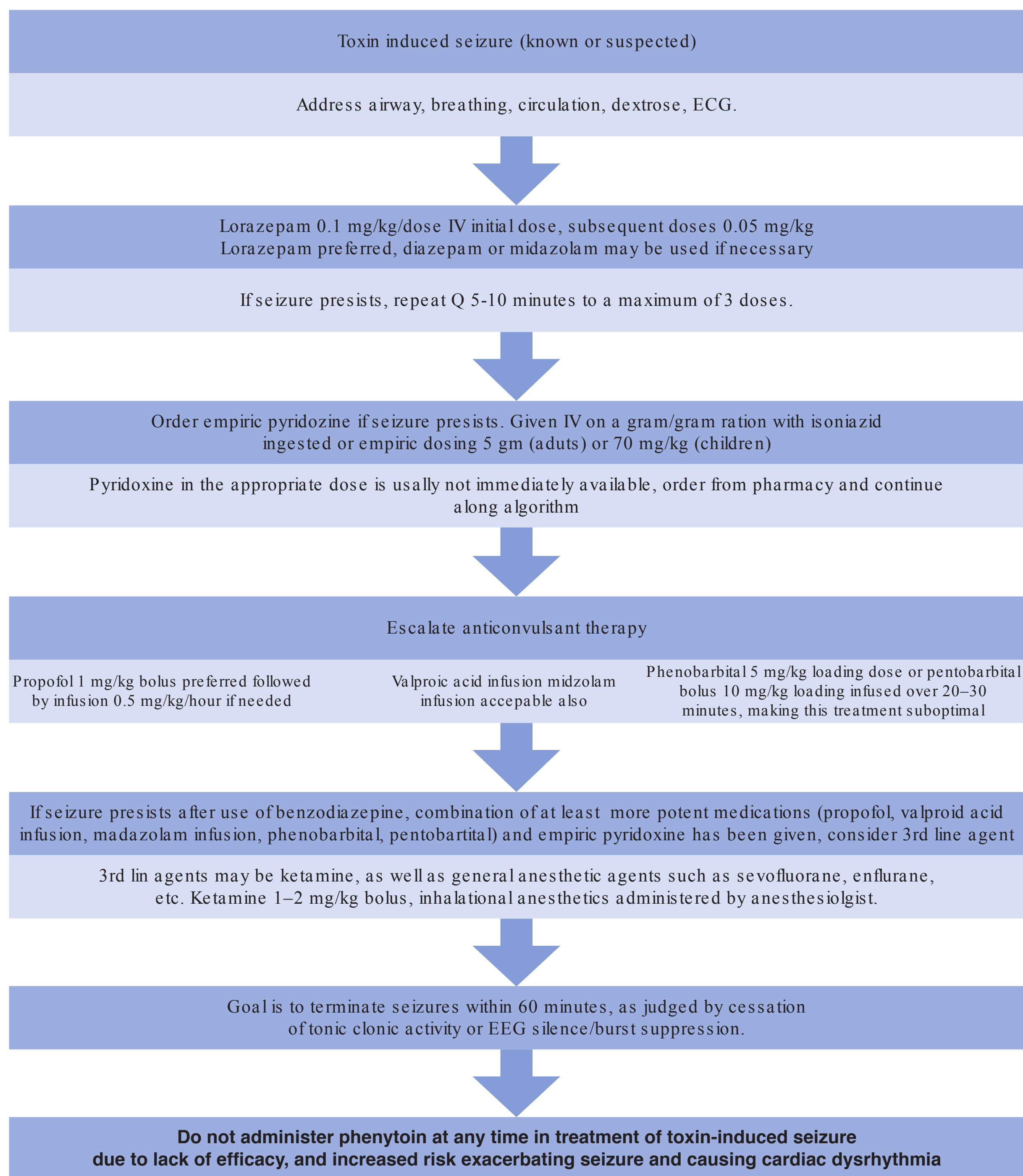


FIGURE 50-1 Management of toxin-induced seizure.

The traditional algorithm for management of seizures or status epilepticus has been three doses of a benzodiazepine, after which use of a barbiturate begins (Figure 50-1). Due to the advent of highly effective medications such as propofol and valproic acid, these newer medications may be used instead of barbiturates after initial use of benzodiazepines fails. Decision to use barbiturates or newer medications such as propofol or valproic acid is based on clinician preference and comfort.

Propofol

Propofol is extraordinarily rapid in its ability to terminate seizure activity, and its activity as both a γ -aminobutyric acid (GABA) agonist and NMDA antagonist makes it the most useful and preferred agent for toxin-induced status epilepticus. We recommend propofol for use after failure of benzodiazepine therapy by administration of 1 mg/kg IV followed by

repeated boluses of propofol infusion at 0.1–0.3 mg/kg/min titrated to clinical effect.

Barbiturate

Barbiturate loading can be accomplished with pentobarbital 5 mg/kg IV or phenobarbital 10–20 mg IV, typically loaded over 20 minutes.

Valproic Acid or Midazolam

Valproic acid works by GABA agonism; dosing is 25 mg/kg infused over 5–10 minutes. Midazolam is also a GABA agonist; loading and infusion dosing are loading dose 0.15 mg/kg IV followed by infusion of 1 mcg/kg/min. Every 5 minutes of seizure activity, double infusion rate to maximum rate of 16 mcg/kg/min. If continuous seizure, this would take 20 minutes to reach the maximum infusion dose rate.

Respiratory depression and need for endotracheal intubation should be anticipated when administering a barbiturate subsequent to a benzodiazepine or with any therapeutic propofol use. For this reason, administration of propofol with planned endotracheal intubation is reasonable. Unless continuous EEG monitoring is available, use of any long-acting paralytic agent is not recommended since it may mask seizure activity and prevent appropriate escalation of pharmacologic therapy if seizures continue. Due to its brief duration of activity, succinylcholine may be used as a paralytic if there are no contraindications such as significant hyperkalemia.

Third-Line Anticonvulsants

Other medications that may be employed are third-line agents levetiracetam³⁷ and ketamine.³⁸

Levetiracetam's mechanism of action is unknown, and therefore it is less desirable for use in toxin-induced seizures because there is potential, as with phenytoin, to exacerbate seizures or to increase morbidity and mortality. Levetiracetam dosing is 20–40 mg/kg IV diluted in 100 mL of saline and infused over 15 minutes.

Ketamine has the potential to dissipate seizures by a different mechanism of action, NMDA antagonism, than other medications reviewed here, most of which work by GABA agonism. Little data on ketamine therapy for status epilepticus exist. Dosing is initial 1 mg/kg IV bolus, followed by 0.05–0.1 mg/kg/min infusion. Further treatment may involve general anesthetic agents administered by an anesthesiologist.

Management of seizures from other toxin-induced phenomena such as hyponatremia or hypocalcemia may be carried out in the typical fashion.

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Acetaminophen Overdose

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INTRODUCTION AND BACKGROUND

Acetaminophen is the most widely used analgesic and a commonly used antipyretic. It has been available as an over-the-counter formulation for more than 50 years and is exceptionally safe when used according to manufacturer directions.¹ Unfortunately, toxic levels can make it a silent and lethal killer because overdose may initially present with few, if any, symptoms.^{2–5} If not promptly discovered and treated, acetaminophen toxicity can lead to liver failure and death unless a successful liver transplant is performed.^{5–11}

Acetaminophen is packaged under multiple names and is a component of many different medicinal products around the globe. In the United States it is commonly sold as the brand name Tylenol® whereas in the United Kingdom it is generally sold under the alternate generic names of paracetamol and *N*-acetyl-*p*-aminophenol (APAP).¹²

In the United States, acetaminophen is available in varied doses and forms. Oral dosage formulations include 325 and 500 mg immediate-release as well as 650 mg extended-release products. For all formulations, the adult dose should not exceed 1,000 mg for a single dose or 4,000 mg per day.¹³ Pediatric acetaminophen products are also available in multiple formulations, including concentrated drops, liquid suspensions, suppositories, chewable tablets, and orally disintegrating tablets.^{12,13} Pediatric doses should not exceed 15 mg/kg

per single dose (up to a maximum of 1,000 mg per dose) or 75 mg/kg/day (up to a maximum of 4,000 mg per day).^{12,14,15}

Acetaminophen is found in many over-the-counter and prescription medicines such as Sudafed PE® Severe Cold (acetaminophen, diphenhydramine, and phenylephrine), Percocet® (acetaminophen and oxycodone), and Fioricet® (acetaminophen, butalbital, and caffeine). Unintentional overdose may occur with these combination products because the general public is unaware of the specific medications in such formulations and may inadvertently exceed the maximum single or daily acetaminophen dosage when taking multiple combination products simultaneously.

In an effort to reduce unintentional acetaminophen overdose, the U.S. Food and Drug Administration (FDA) requested that manufacturers limit the strength of acetaminophen in all prescription drug products to 325 mg by January 2014.¹⁶ The FDA subsequently announced in March 2014 that all prescription drug products containing acetaminophen in the U.S. market have been successfully limited to 325 mg per dose unit. These formulation changes do not apply to over-the-counter (OTC) acetaminophen products.

Acetaminophen overdose may be acute or chronic (Figure 51-1). An acute overdose is generally defined as a toxic dose (> 150 mg/kg or > 7.5 g) ingested in < 8 hours. A chronic overdose is also referred to as “repeated supratherapeutic ingestion” and is generally defined as a toxic dose

Type of overdose	
Acute	Chronic
A toxic dose ingested in < 8 hours Rumack nomogram is useful!	A toxic dose ingested in > 8 hours <i>Rumack nomogram <u>not</u> used.</i>
Toxic dose = 150 mg/Kg	

FIGURE 51-1 Acute versus chronic overdose.

taken over > 8 hours.^{17,18} Overdose may be accidental, as is frequently the case with pediatric overdoses, or intentional, as is the case with suicide attempts.

Overdose is defined as any dosing regimen over the recommended 4 g per day. However, for the average 70 kg adult, the acetaminophen ingestion necessary for hepatotoxicity is much higher—150 mg/kg, or approximately 10.5 g. Thus, approximately 20 extra strength (500 mg) pills are potentially lethal for the average patient.^{2,19} Since acetaminophen is readily available, it is an easy overdose agent for suicide attempts.

Additionally, pediatric dosing is easy to confuse and can often lead to therapeutic error. Pediatric dosing is particularly problematic since the infant's formulation (100 mg/mL) is more than three times the concentration of the children's formulation (32 mg/mL).¹² Thus, equal volumes contain significantly different milligrams of acetaminophen, creating a high potential for overdose.

The risk of hepatotoxicity after an acute acetaminophen overdose is determined using the Rumack–Matthew nomogram (Figure 51-2).^{2,4,19–23} This easy-to-use graph allows providers to assess risk based on plasma acetaminophen concentration and time post-ingestion. The antidote, *N*-acetylcysteine (NAC), is administered if there is a possible risk of hepatotoxicity.^{2,4,19–30} This is discussed in detail further in this chapter.

EPIDEMIOLOGY

Acetaminophen is a frequently used analgesic throughout the world, particularly in the United States, Canada, and Europe.^{26,31,32} In the United States, it is the most commonly used prescription and over-the-counter drug, taken either alone or as a multidrug product, with more than 50 million people using it every week.³² In the United States, analgesics are the most common medication class associated with poisoning and account for nearly 25% of overdose-related deaths, of which half are due to ingestions of a product that contains acetaminophen.³¹

In 2012, U.S. Poison Control Centers reported 309,618 exposures to analgesics, of which 64,544 were acetaminophen exposures in combination with another drug, and 71,766 were exposures regarding acetaminophen alone.³¹ Additionally that year, acetaminophen (alone or in combination) was responsible for 342 deaths—nearly 12% of all poison-related deaths in the United States.³¹

Acetaminophen overdose places a large burden on the health care system because it is responsible for more than

70,000 visits to health care facilities.^{31–33} If untreated within 24 hours, acetaminophen poisoning has significant morbidity and mortality risks. Patients who initially present with hepatic failure have a mortality rate of 20–40%.³³

Acetaminophen overdose is now the number one cause of acute liver failure in the United States.^{34–38} This morbidity and mortality can be avoided when promptly treated.^{33,39,40} As discussed later, the antidote, NAC, is nearly 100% effective if given within 8 hours, is often useful up to 12–24 hours, and occasionally may even prove useful after 24 hours.^{23–30}

PATHOPHYSIOLOGY

Acetaminophen is rapidly absorbed in the gastrointestinal tract. Peak serum levels occur within 90 minutes following ingestion of immediate-release formulations. The drug is primarily metabolized by the liver.^{2,4,6–11,35,41}

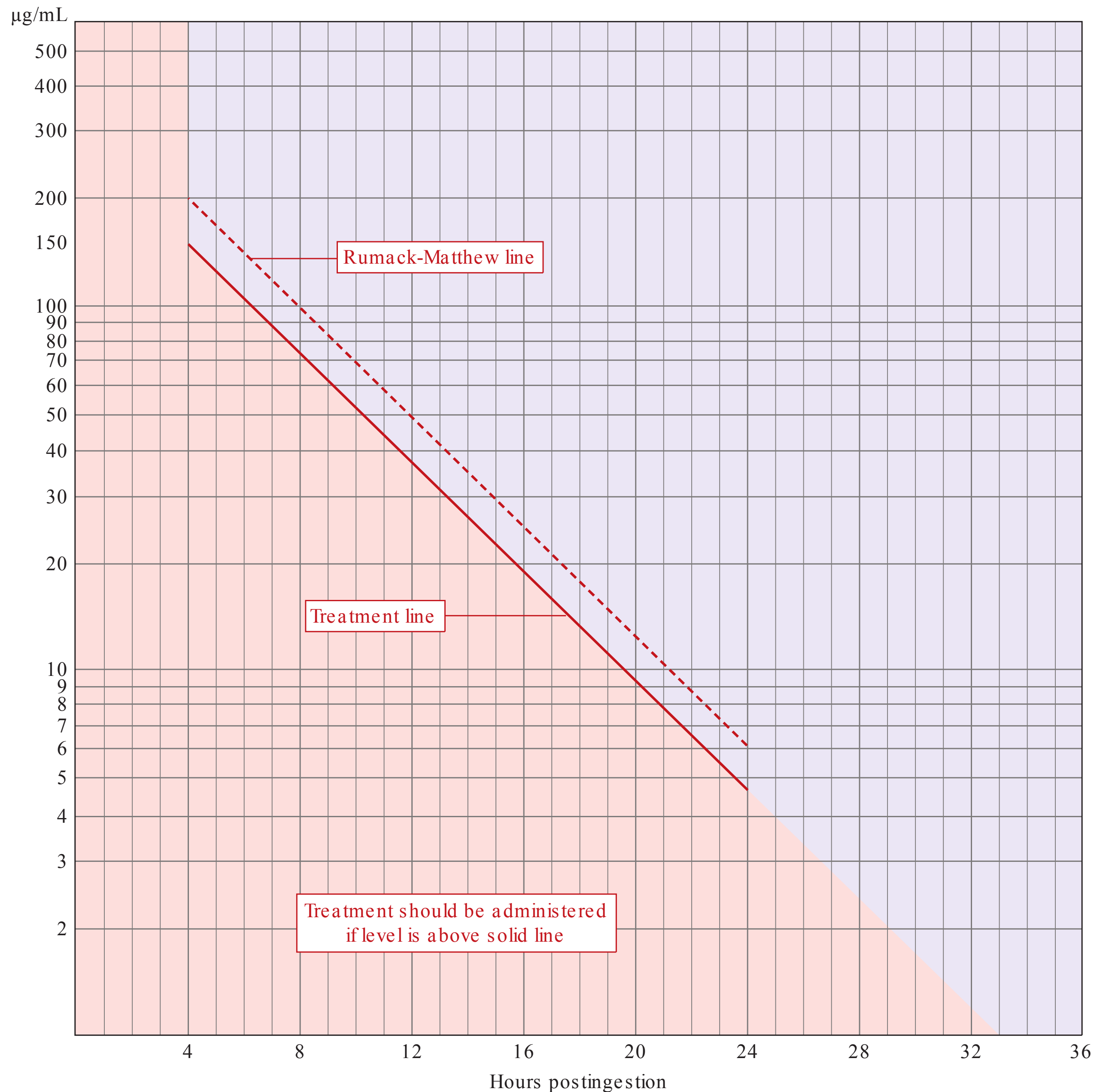
The drug itself does not directly damage the liver. Rather, damage is caused by acetaminophen metabolism when *N*-acetyl-*p*-benzoquinone imine (NAPQI), a hepatotoxic metabolite, is produced (Figure 51-3).^{2,4,6–11,35}

Under normal metabolic circumstances, approximately 5–15% of a therapeutic dose of acetaminophen is metabolized by the cytochrome P450 enzyme system (primarily CYP2E1) to the NAPQI metabolite. This small amount of NAPQI is rapidly conjugated with glutathione to form non-toxic cysteine and mercapturic acid metabolites.^{2,4,6–11,35,41,42} However, in the setting of acetaminophen overdose, glutathione stores are depleted, and there is an accumulation of NAPQI that causes hepatic injury and cell death.

The American College of Emergency Physicians (ACEP) defines hepatotoxicity after acetaminophen overdose as any increase in the aspartate aminotransferase (AST) level.⁴⁰ Severe hepatotoxicity is generally defined as an AST level of > 1,000 IU/L.³⁸ Acute liver failure is defined as severe hepatotoxicity with hepatic encephalopathy (Figures 51-4 and 51-5).⁴⁰

If glutathione can be replenished, then NAPQI can be metabolized into a nontoxic form that is then excreted via the kidneys. Cysteine is the rate-limiting substrate necessary for the creation of glutathione, which is formed via the synthesis of cysteine, glutamate, and glycine.⁴³ NAC is a substance that provides an absorbable form of cysteine that can then be hydrolyzed to synthesize glutathione. This additional glutathione is then used to detoxify the enormous levels of NAPQI created during acetaminophen overdose.

There are several factors that appear to lessen hepatotoxicity. Acute ethanol ingestion is reported to potentially reduce the hepatotoxic effects of acetaminophen in at least one prospective study; the potential mechanism of this protective effect is postulated to be ethanol competition with acetaminophen for CYP2E1 metabolism.^{44,45} Others suggest that coingestion of opioid analgesics may be a protective factor in the development of hepatic encephalopathy (OR 0.26; CI 0.07, 0.96).⁴⁶ Phenytoin, initially thought to cause hepatotoxicity, is now suggested to be potentially hepatoprotective by increasing glucuronidation that facilitates the metabolism



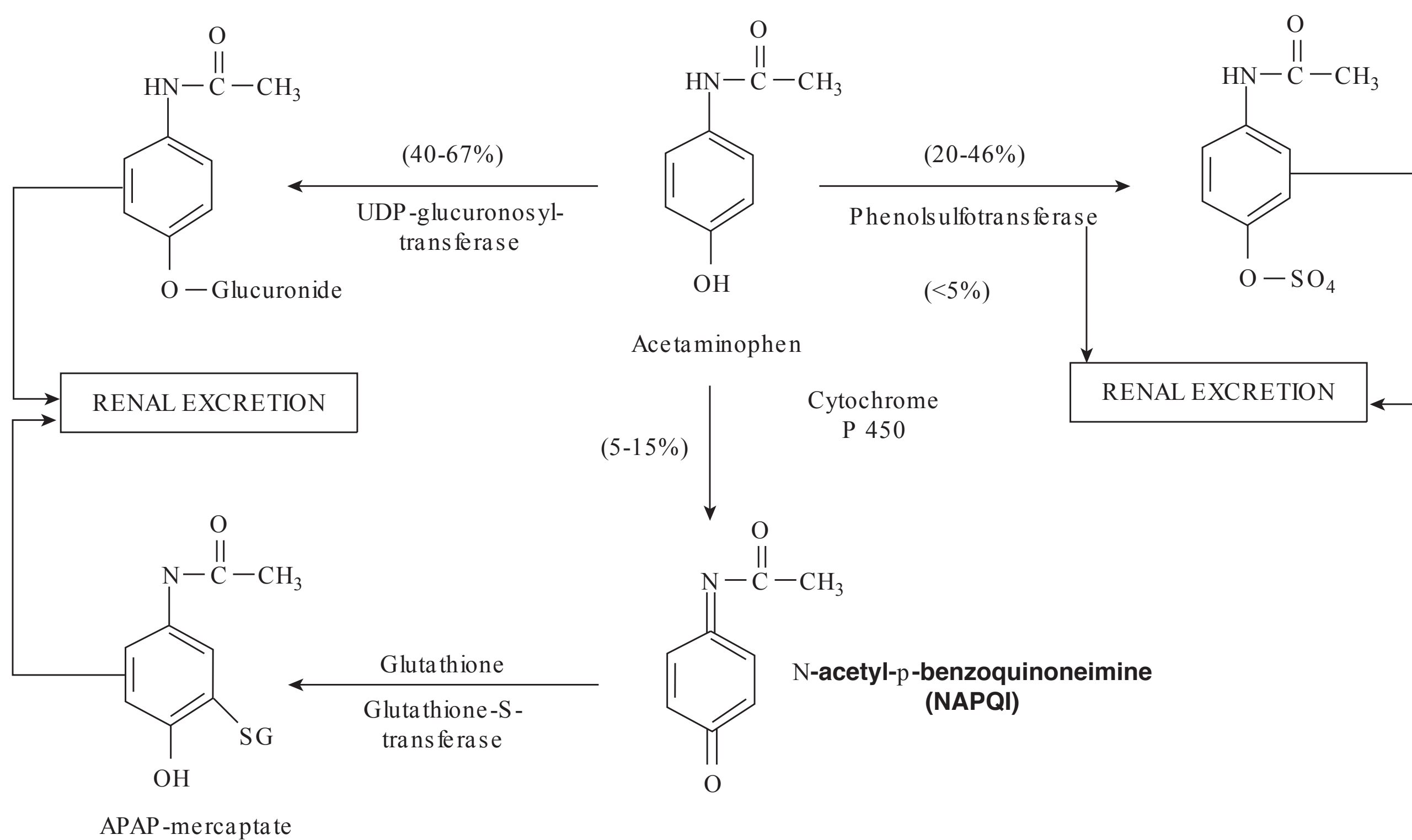
Nomogram: acetaminophen plasma concentration vs time after acetaminophen ingestion. The nomogram has been developed to estimate the probability of whether a plasma acetaminophen concentration in relation to the interval postingestion will result in hepatotoxicity and, therefore, whether acetylcysteine therapy should be administered.

Cautions for use of this chart:

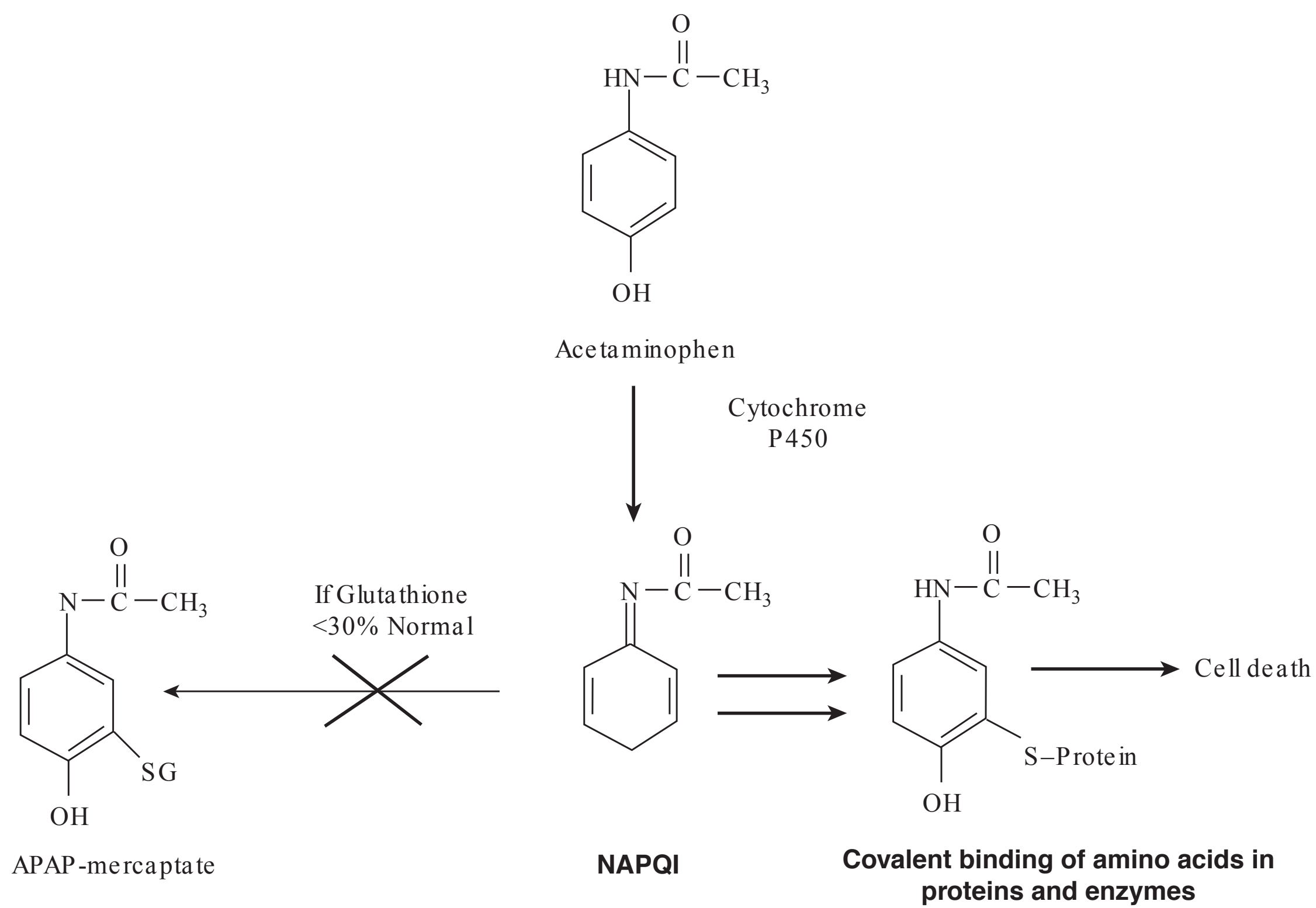
1. Time coordinates refer to time postingestion.
2. Graph relates only to plasma concentrations following a single, acute overdose ingestion.
3. The treatment line is plotted 25% below the Rumack-Matthew line to allow for potential errors in plasma acetaminophen assays and estimated time from ingestion of an overdose.

For additional emergency information, call your regional poison control center. For special consultation, call the Rocky Mountain Poison and Drug Center toll-free number, 1-800-525-6115, available 24 hours a day.

FIGURE 51-2 Rumack–Matthew nomogram. Guidelines for the management of acetaminophen overdose (www.tylenolprofessional.com). (Adapted with permission from Rumack BH, Matthew H: Acetaminophen poisoning and toxicity, *Pediatrics* 1975 Jun;55(6):871–876.)



A



B

FIGURE 51-3 (A and B) Acetaminophen metabolism. (Reproduced with permission from Tintanelli JE, Kelen GD, Stapczynski JS: *Tintinalli's Emergency Medicine: A Comprehensive Guide*, 6th edition. New York: McGraw-Hill Inc; 2004.)

Stages of acetaminophen toxicity			
Stage	Time	Liver effects	Signs & Symptoms
1	0-24 hrs	Preclinical	<ul style="list-style-type: none"> • General malaise • Nausea and vomiting • Diffuse abdominal pain • Possibly asymptomatic • Minimal signs and symptoms • Normal liver function tests, possibly
2	24-72 hrs	Hepatotoxicity	<ul style="list-style-type: none"> • RUQ pain, possibly • Clinically asymptomatic, possibly • AST and ALT begin to rise, and possibly bilirubin • Coagulopathy studies (PT, PTT, INR) may increase, if severe injury
3	72-96 hrs	Hepatic failure with encephalopathy	<ul style="list-style-type: none"> • Liver function tests peak • Clinical signs and symptoms of liver failure are evident, including: <ul style="list-style-type: none"> • Jaundice • Vomiting • GI upset • Coagulopathy • Encephalopathy • Metabolic acidosis • Pancreatitis, possibly • Acute renal failure, possibly
4	> 96 hrs	Survival or death	<ul style="list-style-type: none"> • Full resolution of hepatotoxicity, <u>or</u> • Multi-organ failure and death

FIGURE 51-4 Stages of acetaminophen toxicity.

of acetaminophen into nontoxic metabolites.⁴⁷ These studies are clinically limited; thus, further research is necessary to fully understand these relationships and the underlying mechanisms of action.

Multiple factors appear to worsen hepatotoxicity during acetaminophen overdose. These include cirrhosis, chronic alcohol abuse, coingestions, certain preventable conditions, other medications, and dehydration and/or malnutrition.^{37,48}

Nearly one third of all patients who overdose on acetaminophen ingest other substances—often alcohol or opiates. Certain coingestions appear to be independent risk factors for the development of hepatic encephalopathy, renal dysfunction, and death or liver transplantation.⁴⁶ Preventable conditions also appear to increase mortality among patients found to be hepatotoxic secondary to acetaminophen overdose. These include attempted suicide, substance abuse, and trauma.^{36,37}

The relation between chronic, heavy alcohol abuse and acetaminophen use has been debated for decades. Chronic alcohol consumption can result in up-regulation of CYP2E1 and decreased glutathione synthesis, which may result in an increased risk of hepatotoxicity.⁴⁹ Although alcoholics are likely to be at a greater risk for hepatotoxicity following acetaminophen overdose, there is little to no evidence to suggest such toxicity when taking therapeutic doses of acetaminophen.⁴⁷ Dehydration and/or malnutrition may compound the relationship between alcoholism and acetaminophen toxicity during acute ingestions; however, further research is needed to better understand these potential risk factors.^{37,47}

HISTORY

Any patient presenting to the Emergency Department receives a primary survey: airway, breathing, circulation,

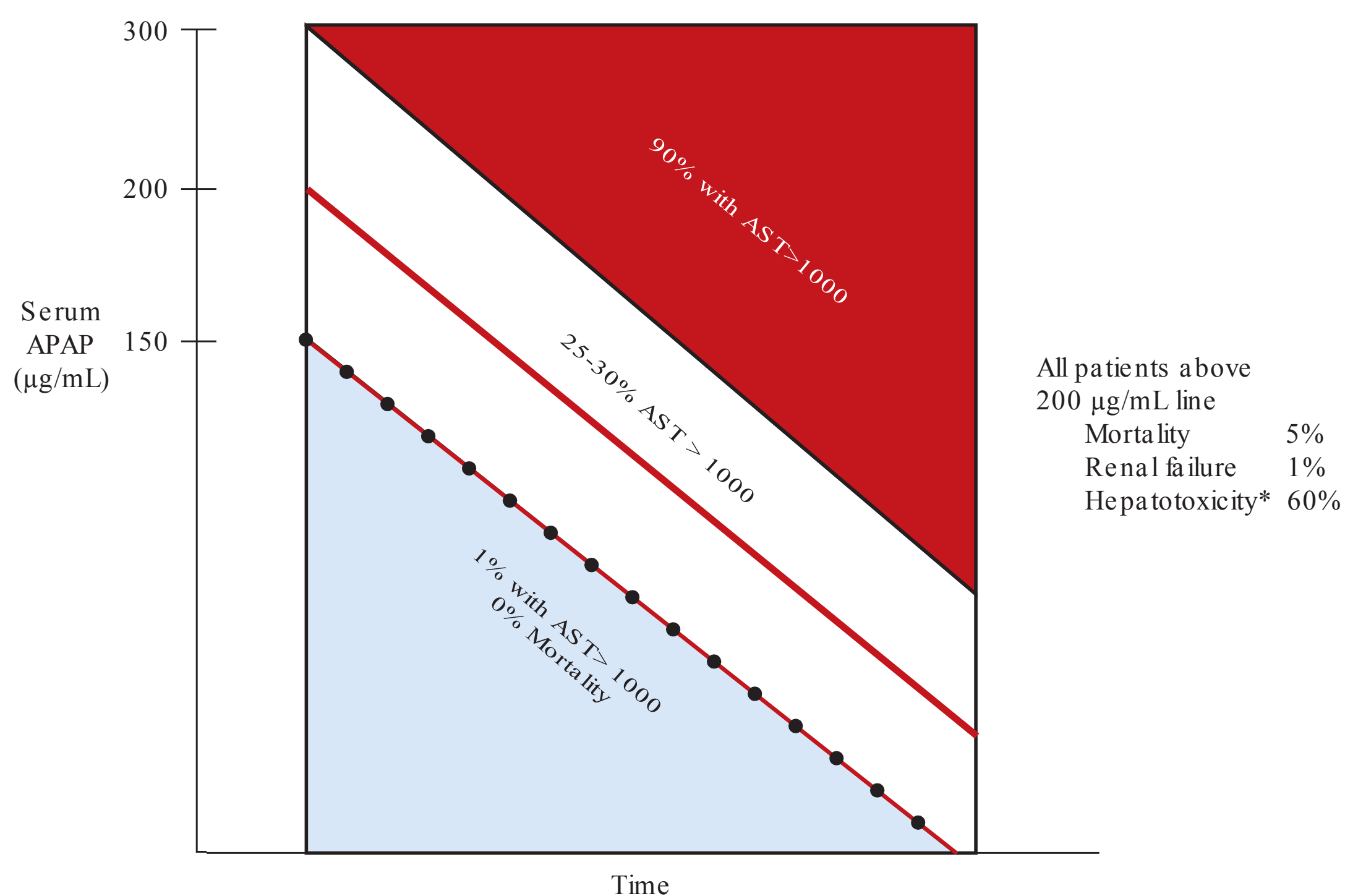


FIGURE 51-5 Outcome of acetaminophen-poisoned patients (based on AST). *Defined as AST > 1000. (Adapted with permission from Smilkstein MJ, Knapp GL, Kulig KW, et al. Efficacy of oral N-acetylcysteine in the treatment of acetaminophen overdose, *N Engl J Med*. 1988 Dec 15;319(24):1557–62.)

disability/dextrose, and exposure. In a poisoned patient, the resuscitation and diagnosis occur simultaneously by utilizing all members of the health care team. It is imperative to receive a thorough history from emergency medical services (EMS) personnel, as well as from family, friends, and/or bystanders.

The history should be obtained from both the patient and a corroborator. Questions should address the time of ingestion, the specific substances, the route of ingestion (PO, IV, PR, inhaled), and the exact amounts. Regardless of historical source, it is imperative to count pills if the bottles are available. Specific to acetaminophen overdose:

- *Were there coingestions?*
- *Were extended-release tablets involved?*
- *Did the patient intend to hurt himself or herself, or was the ingestion accidental?*
- *Was the ingestion acute (i.e., all at once), or was it chronic (generally > 8 hours)?*

The history and physical exam must focus on coingestions, self-harm, homicidal intent, and psychiatric illness. Keep in mind that any attempted suicide must consider acetaminophen overdose among possible coingestions.

STAGES OF ACETAMINOPHEN TOXICITY

The clinical presentation and progression of acetaminophen overdose are generally categorized into four stages (Figure 51-4):

Stage 1 (0–24 hours): *Preclinical toxic effects* with minimal signs and symptoms, possibly asymptomatic, and often normal liver function tests. The vague, nonspecific symptoms of this stage might include nausea and vomiting, diffuse abdominal pain, and general malaise.

Stage 2 (24–72 hours): *Hepatic injury (hepatotoxicity or “latent phase”)*. Patients may begin to develop RUQ pain, although sometimes they are clinically asymptomatic. AST and ALT begin to rise, and possibly bilirubin. If injury is severe, then coagulation studies (PT, PTT, INR) may increase.

Stage 3 (72–96 hours): *Hepatic failure with encephalopathy or “hepatic phase.”* Liver function tests peak, and clinical signs and symptoms of liver failure are evident, including jaundice, vomiting and gastrointestinal pain, coagulopathy, encephalopathy, metabolic acidosis, and possibly acute renal failure and/or pancreatitis.

Stage 4 (> 96 hours): *Survival or death (“recovery phase”).* Either there is full resolution of hepatotoxicity or fulminant liver failure progresses to multiorgan failure and death.

PHYSICAL EXAM

Patients presenting with acetaminophen overdose must be completely undressed and examined from head to toe. It is useful to use security and/or police at the bedside for staff

safety and the collection of patient belongings. This includes a thorough inspection of substances or objects that might be in pockets or hidden on the patient’s body. Providers should be extremely cautious for dirty needles, sharp objects, and/or other contaminants.

As part of the primary survey, a blood glucose check is essential, as is an inspection of the oropharynx. It may be useful to inspect the rectal cavity for any retained substances (i.e., tablets, drug balloons, or other paraphernalia) or gastrointestinal bleeding.

An acute acetaminophen overdose will generally have few, if any, symptoms. Those symptoms that do exist may be vague and nonspecific and may include mild abdominal pain or cramping, nausea and vomiting, and general malaise. Massive, acute overdose may, on occasion, present initially with metabolic acidosis and coma, even before the development of hepatotoxicity. Usually such presentation is caused by coingestions, frequently alcohol or opiates.

Coingestions often create additional signs and symptoms elicited during the physical exam of an acetaminophen overdose. Classic toxidromes may be encountered when additional substances are ingested: opioid, sympathomimetic, cholinergic, anticholinergic, or others.

Delayed presentation of acute acetaminophen overdose may present with more severe symptoms of hepatotoxicity, such as jaundice, RUQ pain and tenderness, and possibly altered mental status.

LABORATORY DATA AND RELATED STUDIES

Applicable laboratory data and related studies should be ordered as listed in Figure 51-6. The Rumack–Matthew nomogram is the most important tool used to guide clinical decisions about the treatment of acute acetaminophen overdose up to 24 hours after ingestion. It has potential use for the ingestion of extended-release preparations, as discussed later in the chapter. The nomogram may not be used under the following circumstances⁴⁰:

- Unknown time or duration of ingestion
- Chronic ingestion (repeated supratherapeutic)
- Delayed presentation (> 24 hours after ingestion)

The following serum acetaminophen levels are toxic according to the nomogram (Figure 51-2):

- 4-hour level > 150 mcg/mL
- 6-hour level > 106 mcg/mL
- 8-hour level > 75 mcg/mL
- 24-hour level > 4.6 mcg/mL

TREATMENT GUIDELINES

There are four general treatment modalities for acetaminophen overdose: (1) decrease absorption, (2) increase elimination, (3) administer antidote, and (4) undertake liver transplantation.^{26,50}

Laboratory data & related studies	
Lab Test	Expected Findings
Acetaminophen level	Check at 4-hours post-ingestions. Toxic <i>if > 150 micrograms per deciliter</i> Repeat at 8-hours if extended release tablets with a normal 4-hour level. Toxic <i>if > 75 micrograms per deciliter</i>
Electrolytes, BUN/Cr, and glucose	Metabolic acidosis (with large ingestions).
Liver function tests	AST usually rises first, then ALT and bilirubin.
Coagulation studies	Rise with hepatotoxicity and liver failure.
Urinalysis and UhCG	Proteinuria and hematuria, if acute tubular necrosis, in conjunction with liver failure.
If suicide attempt and/or altered mental status then consider: <ul style="list-style-type: none"> • Aspirin level • Alcohol level • Complete blood count (CBC) • Arterial/venous blood gas (pH and lactate may predict mortality) • Electrocardiogram (prolonged QT, or other changes, seen with co-ingestions) • Radiology studies, as indicated 	

FIGURE 51-6 Laboratory data and related studies.

In the Emergency Department, one must first complete a primary survey and ensure that airway, breathing, and circulation are appropriately established. Oxygen, IV access, cardiac monitor, and pulse oximetry are ordered as needed.

Nasogastric tubes (NGT) are of limited clinical benefit, if any, in the setting of acetaminophen overdose.^{26,50,51} Some facilities continue to use this practice, although it is not supported by evidence-based guidelines. Given the risk for inducing vomiting and potentially compromising the airway, most physicians have abandoned the use of an NGT. There is a limited argument for the continued use of an NGT if the ingestion occurs < 1 hour prior to arrival or if dangerous coingestants were consumed. Under these circumstances, it is argued that gastric lavage may remove some of the pill fragments remaining in the stomach, thereby preventing further absorption.

The medications used to treat acetaminophen overdose consist of activated charcoal to decrease absorption and NAC as an antidote to increase elimination, with antiemetics used as clinically indicated.

Gastrointestinal decontamination is primarily achieved with activated charcoal. There is moderate evidence that significant benefit occurs if this is given within 1 hour of the ingestion.^{26,51} When activated charcoal is administered 2–4 hours post-ingestion, pharmacokinetic studies in human volunteers demonstrate a smaller reduction in acetaminophen absorption of questionable clinical significance. Although the potential for benefit beyond 1 hour post-ingestion cannot be excluded, the majority of evidence supports the recommendation to administer charcoal only within 1 hour of a potentially toxic acetaminophen ingestion.^{52–54} Superactivated charcoal may offer some detoxification benefit when given within 3 hours

post-ingestion; however, this is not typically stocked in many Emergency Departments.⁵⁵ There is no clinical benefit to the use of syrup of ipecac, and it should no longer be used in acetaminophen overdose.^{50,56} Antiemetics are used symptomatically to prevent aspiration and airway compromise.

The most important treatment in acetaminophen overdose is the antidote NAC—manufactured under the brand names Mucomyst® and Acetadote®.^{23,26,28,30,39} It works via the pathways discussed earlier (Figure 51-3).

When administered within 8–10 hours post-ingestion, there is no difference in the efficacy between the oral and IV preparations.^{24,28} Historically, the oral preparation was used; however, the IV preparation was approved by the FDA in 2004 and has subsequently become the primary preparation.^{57–59} Many institutions now use the IV form because of a decreased treatment time, a decreased likelihood of complications secondary to vomiting, and a decreased hospital stay and associated costs.^{26,60} IV NAC should also be used if treatment is > 10 hours post-ingestion or if underlying conditions prevent oral use.^{24,25} IV NAC is preferred in the setting of fulminant hepatic failure. There is some evidence that patients with asthma or atopic dermatitis should receive oral therapy because of the decreased risk of anaphylactoid reaction; however, this is not necessarily the current standard of care.^{24,57,61} Regardless of the route of administration, acetylcysteine is most effective when administered within 8–10 hours post-ingestion.

Over the past decade, a significant change in treatment has occurred as the IV form of NAC has become the standard over PO. This decreases total time of treatment and also reduces risk of aspiration from vomiting (Figures 51-7 to 51-9).

Intravenous (IV) NAC dosing for adult and pediatrics Total of 3-doses over 21-hours				
<i>Dose</i>	<i>Time</i>	<i>Amount</i>	<i>Diluent</i>	<i>Infusion Rate</i>
1 st	Immediate IV loading dose	150 mg/Kg	Adult 250 mL of D5W Pediatric (>20 kg but <40 kg): 100 mL (≤20 kg): 3 mL/kg	Over 1-hour
2 nd	Immediately after 1st dose	50 mg/Kg	Adult 500 mL of D5W Pediatric (>20 kg but <40 kg): 250 mL (≤20 kg): 7 mL/kg	Over 4-hours
3 rd	Immediately after 2nd dose	100 mg/Kg	Adult 1 L of D5W Pediatric (>20 kg but <40 kg): 500 mL (≤20 kg): 14 mL/kg	Over 16-hrs

Oral (PO) NAC dosing for adult and pediatrics Total of 18-doses over 72-hours				
<i>Dose</i>	<i>Time</i>	<i>Amount</i>	<i>Route</i>	<i>Considerations</i>
1 st	Immediate PO loading dose	140 mg/Kg	Oral	Anti-emetic may be helpful
2 nd – 18 th	Every 4-hours after loading dose	70 mg/Kg	Oral	Anti-emetic may be helpful

FIGURE 51-7 NAC dosing (PO and IV) for adult and pediatrics.

The IV dosing for adults (patients > 40 kg) consists of the following protocol: Acute ingestions (8–10 hours after ingestion) receive an IV loading dose of 150 mg/kg (body weight) diluted in 200 mL of D5W infused over 1 hour. Two maintenance doses are then initiated as follows: The first maintenance dose (started immediately after the loading dose) is 50 mg/kg diluted in 500 mL of D5W infused IV over 4 hours. The second maintenance dose (started immediately after the first maintenance dose) is 100 mg/kg diluted in 1,000 mL of D5W infused IV over 16 hours. The total of the three doses administered is 300 mg/kg over 21 hours.

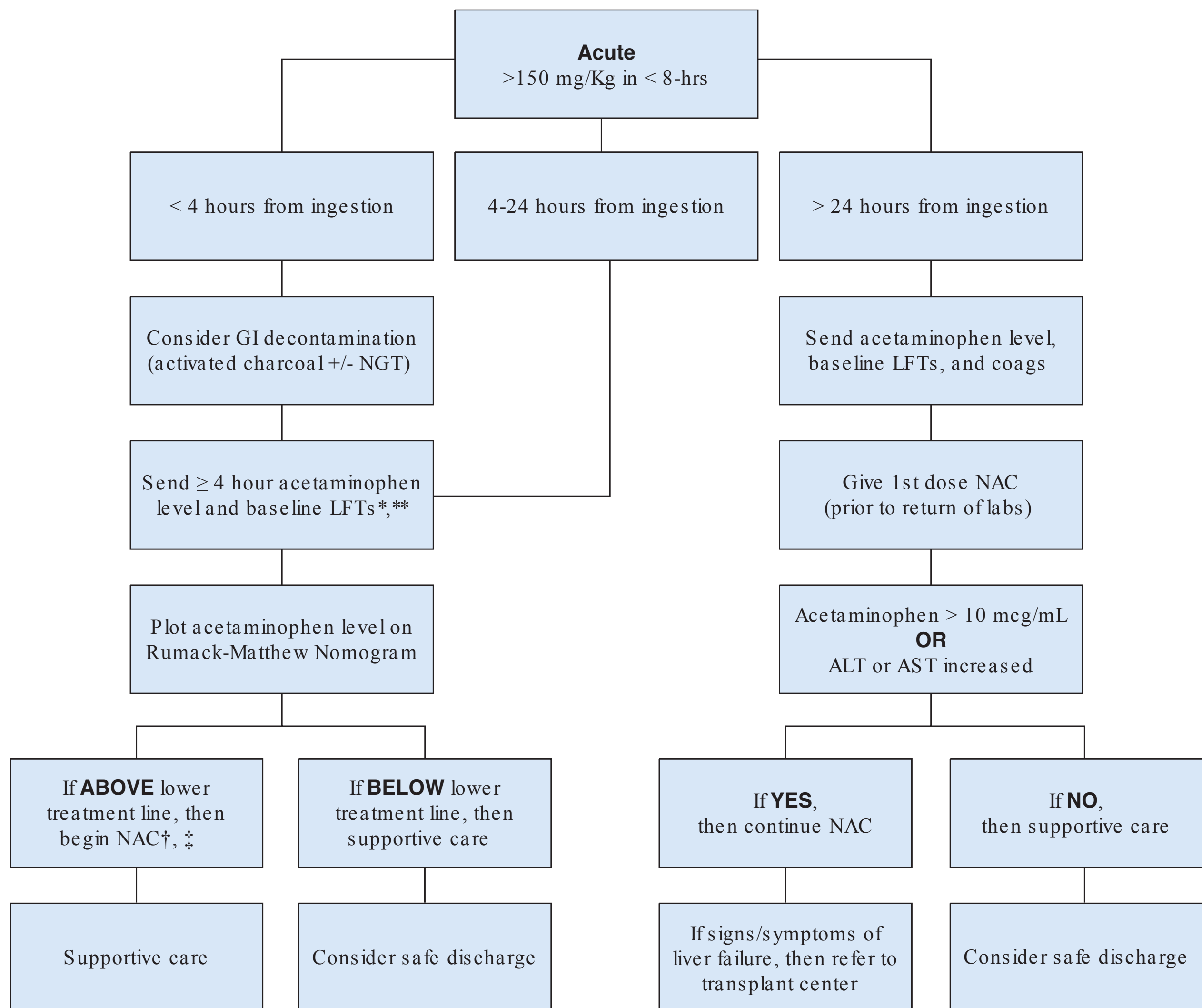
The oral loading dose for adults is 140 mg/kg once, and then maintenance doses of 70 mg/kg starting 4 hours after loading dose and repeated every 4 hours for a total of 17 additional doses. A total of 18 doses is administered equaling 1330 mg/kg over 72 hours.^{39,62,63}

The IV dosing for adult chronic ingestion or late presentation (> 8 hours after ingestion) is an IV loading dose of 140 mg/kg

diluted in 500 mL D5W infused over 1 hour. Maintenance doses are then initiated as follows: 70 mg/kg diluted in 250 mL of D5W infused IV over at least 1 hour. This maintenance dose is repeated every 4 hours for at least 12 doses. Total treatment time is at least 48 hours.⁶⁴ If fluid restriction is required, then the total volume of D5W may be decreased.

The IV dosing for pediatrics (patients < 40 kg) is the same as the adult protocol, except the volume of D5W is decreased (Figure 51-7). The oral dosing protocol for pediatrics is the same as the preceding adult protocol.

Several additional literature reports describe alternative acetylcysteine regimens for acute acetaminophen ingestions consisting of shortened courses of oral therapy (< 72 hours) as well as extended intravenous therapy beyond 21 hours in selected patients. However, the absence of prospective comparator trials of these alternative acetylcysteine regimens in addition to the heterogeneity of patient populations evaluated poses significant challenges when identifying



Guidelines For The Management Of Acetaminophen Overdose at www.tylenolprofessional.com states:

* Plasma acetaminophen levels drawn less than 4 hours post-ingestion may not represent peak levels.

** With the extended-release preparation, plasma acetaminophen levels drawn less than 8 hours post-ingestion may not represent peak levels. Draw a second level 4 to 6 hours after the initial level was drawn. Acetylcysteine treatment should be initiated and continued until acetaminophen assay results are available.

† Acetylcysteine can be withheld until acetaminophen assay results are available as long as initiation of treatment is not delayed beyond 8 hours post-ingestion. If more than 8 hours post-ingestion, start acetylcysteine treatment immediately.

‡ With the extended-release preparation, provide acetylcysteine treatment if either level plots above the lower treatment line.

FIGURE 51-8 Treatment guidelines for acute acetaminophen ingestion.

appropriate patients for alternative treatment regimens. Additionally, some experts recommend extending treatment courses beyond the FDA-approved treatment regimen durations in the setting of ongoing hepatotoxicity and/or acute liver failure. Consultation with a medical toxicologist and/or Poison Control Center is advisable considering that medical care may need to be individualized for specific patients.^{63,65}

All patients treated with NAC must be admitted to the hospital for further treatment and evaluation. Any patient presenting with an overdose secondary to a suicide attempt must be evaluated by psychiatry.

RENAL INSUFFICIENCY AND HEPATIC FAILURE

Dose-dependent hypokalemia has been observed, although it tends to be more profound at higher levels of acetaminophen toxicity.^{66,67} It is unclear if this is related to acetaminophen or other confounding factors. One study suggests a renal effect of unclear etiology that causes kaliuresis within the first 24 hours after ingestion.⁶⁷ This occurs regardless of NAC treatment and is independent of vomiting. The treatment is to replace potassium accordingly.

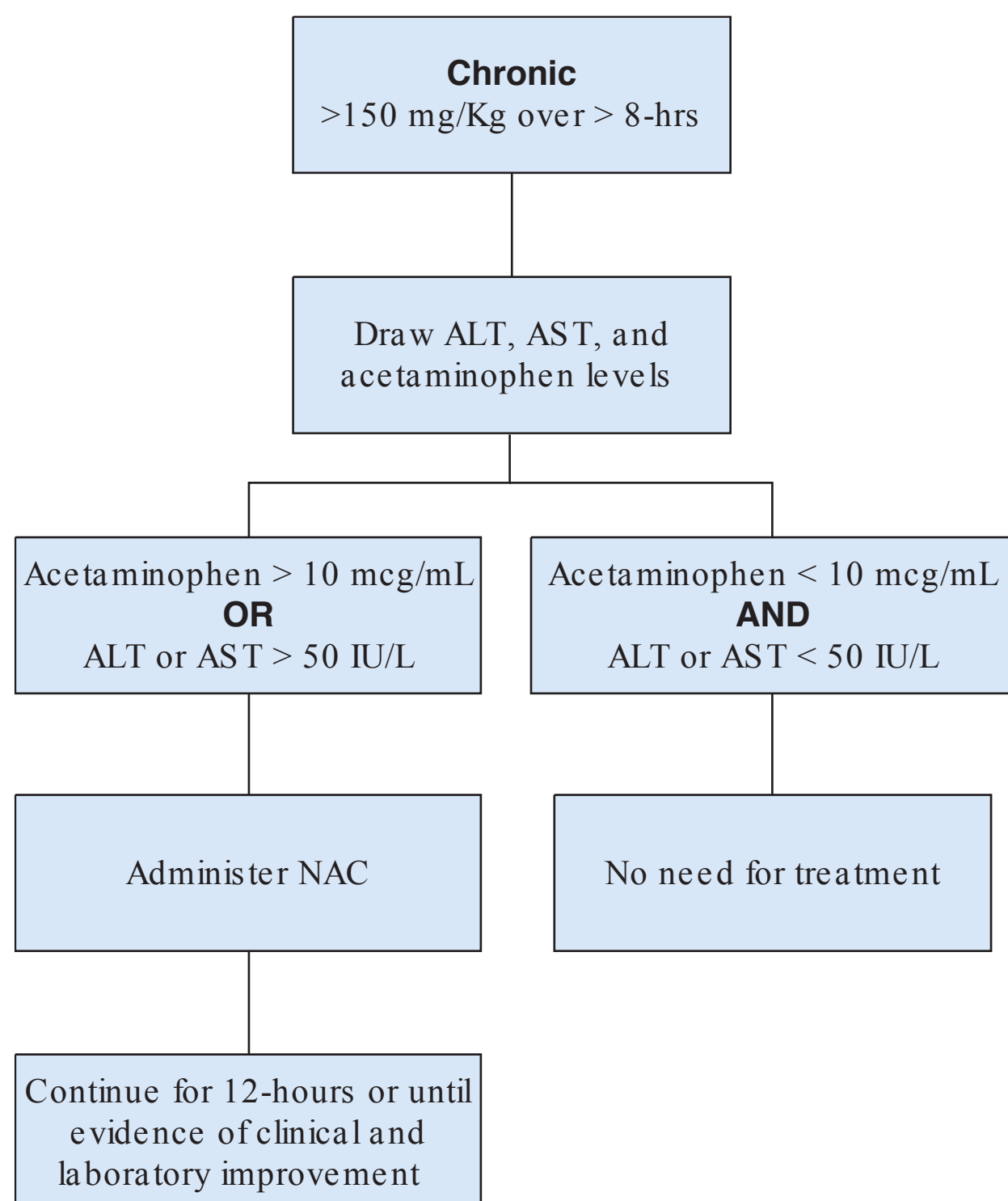


FIGURE 51-9 Treatment guidelines for chronic acetaminophen ingestion.

Renal insufficiency occurs in 1–2% of patients, generally among the more severe ingestions.⁶⁸ One study suggests nephrotoxicity is higher in adolescents, possibly as high as 9%, although further research is indicated.⁶⁹

Fulminant liver failure may lead to significant acidosis, coagulopathy, cerebral edema, and/or multiorgan system failure.⁷⁰ Each of these findings must be addressed accordingly and is frequently resolved in the ICU setting. Referral to a liver transplant center is required.

SPECIAL CONSIDERATIONS

Pediatric patients are treated similarly to adults, except the D5W is decreased during the administration of IV NAC.

Pregnant patients are treated similarly to nonpregnant patients.^{25,26,71} There is no increased risk of adverse pregnancy unless there is severe maternal toxicity.²⁵

Extended-release tablets (650 mg pill) are composed of half immediate-release acetaminophen (325 mg/pill) and half extended-release acetaminophen (325 mg/pill). Therefore, there may be a delayed rise in serum acetaminophen levels.^{26,72,73} If the initial 4-hour serum acetaminophen level is *above* the nontoxic range on the Rumack–Matthew nomogram, then treatment with NAC should be immediately initiated. However, if the initial 4-hour serum acetaminophen level is *below* the nontoxic range on the Rumack–Matthew nomogram, then experts suggest that a second serum acetaminophen level and AST/ALT should be repeated 4–6 hours

after the first (8–10 hours post-ingestion) and treated accordingly based on results.^{26,72,73} Treatment with NAC should be initiated if the serum acetaminophen level is > 10 mcg/mL or if serum AST or ALT is elevated.

Delayed presentation, defined as ingestion > 24 hours prior to presentation, requires the immediate initiation of NAC. Laboratory tests should be ordered as listed previously, including acetaminophen level and liver function tests (Figure 51-6). Treatment with NAC should be continued if the serum acetaminophen level is > 10 mcg/mL or if serum AST or ALT is elevated (Figure 51-8).

Chronic ingestion or “repeated supratherapeutic ingestion (RSTI)” is defined as a toxic overdose taken over > 8 hours and requires laboratory tests as previously described, including liver function tests (Figure 51-6). The Rumack–Matthew nomogram may *not* be used in this scenario. NAC should be initiated if the serum acetaminophen level is > 10 mcg/mL or if serum AST or ALT is > 50 IU/L. It should be continued for 12 hours or until evidence of clinical and laboratory improvement substantiates cessation. Treatment with NAC should be considered if the patient has a history of chronic overdose or exhibits signs and symptoms consistent with toxicity (Figure 51-9).⁶⁴

Safe discharge from the Emergency Department may occur, on rare occasions, if the following criteria are met:

- No coingestions
- No significant medical problems
- Observation for 4–6 hours with a normal reevaluation
- Safe acetaminophen levels based on the Rumack–Matthew nomogram
- Psychiatry evaluation and clearance, if suggestion of intentional overdose

PREVENTION

Patients are often unaware that acetaminophen is commonly present in other medicine they are taking—either prescribed or over-the-counter.⁷⁴ As discussed previously, the FDA has already taken action to minimize the risk of unintentional overdoses with prescription acetaminophen products (e.g., Percocet® Vicodin®) by limiting the strength of acetaminophen. Also, multiple studies suggest that limiting the quantity of acetaminophen available in a single over-the-counter purchase generally reduces associated morbidity and mortality from acute and chronic toxicity.^{75,76} Presently, the FDA and Congress are considering additional strategies to reduce the risk of unintentional overdose.

CONCLUSION

Acetaminophen is the most widely used analgesic, and a commonly used antipyretic, that is a potentially silent and lethal killer. If not promptly discovered and treated, acetaminophen overdose may lead to liver failure and death. However, if treated early with the antidote NAC, then survival is nearly 100%. While both oral and intravenous

NAC appear to have similar efficacy, the parenteral route of administration is more frequently utilized. Given the high morbidity and mortality associated with acetaminophen overdose, it is essential that the Emergency Medicine physician have a high index of suspicion for any potentially lethal overdose.

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Salicylate Overdose

(Shawn) Xun Zhong • Andrew Stolbach

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Salicylates have been used since the 19th century.¹ Today, salicylates are used therapeutically throughout the world. The most commonly encountered salicylate is acetylsalicylic acid (aspirin). Other medications include the liniment methyl salicylate (oil of wintergreen) and bismuth subsalicylate, the active ingredient in Pepto-Bismol. Because salicylates are ubiquitous, there is great potential for toxicity, intentional or accidental. In 2012, there were about 19,000 aspirin-alone exposures reported and about 1,500 aspirin coingestions reported to the National Poison Data System.²

PHARMACOKINETICS

At therapeutic concentrations, salicylate ingested is rapidly absorbed into the bloodstream with a peak serum concentration in 1 hour. When gastric contents are present, absorption may be delayed. Eighty to 90% of plasma salicylate is bound to protein, especially albumin. Most salicylate is biotransformed by the hepatic endoplasmic reticulum but about 10% is eliminated unchanged in the urine. Salicylate and its metabolized products are renally eliminated in a pH-dependent manner. The difference between alkaline and acidic urine can cause free excretion to vary from > 30% to as little as 2%.³

In overdoses, plasma peak concentrations are often delayed up to 35 hours, especially when ingesting extended-release and/or enteric-coated tablets.^{4,5} Bezoar may also form, extending the time of absorption and making the time of peak concentration impossible to predict in any given overdose. As salicylate concentration rises above normal, protein binding and hepatic metabolism are saturated. As a result of the saturation, salicylate metabolism changes from first- to

zero-order kinetics,⁶ and a larger portion of the unmetabolized salicylate is excreted in the urine (see Figure 52-1).³

PATHOPHYSIOLOGY OF SALICYLATE POISONING

In plasma, salicylates are in equilibrium between the protonated (uncharged) and unprotonated (charged) forms. Salicylic acid is a weak acid (pK_a 3.5), which means that a majority of the drug exists in the protonated (uncharged) form. In its uncharged form, it can move easily across membranes and deposit into various tissues, most importantly the CNS. At acidic pH, the equilibrium is shifted farther toward the protonated (uncharged) form, increasing the amount of salicylate able to diffuse across the membranes. Conversely, at high serum pH, equilibrium is shifted toward the unprotonated (charged) form. In this charged form, it cannot cross membranes and becomes “trapped” (see Figure 52-2).⁷

Salicylates affect many organ systems. Gastrointestinal effects are prominent, especially in the acute toxicity. Patients may present with nausea and vomiting from gastric mucosal irritation (from decreased prostaglandin production) and from direct salicylate effects on the medullary chemoreceptor zone. Perforation can occur but is uncommon in acute toxicity.

Salicylates affect the CNS. In the brain, salicylates stimulate the medullary respiratory center causing hyperpnea, tachypnea, and respiratory alkalosis.⁸ In severe toxicities, cerebral edema, seizures, and coma can occur.

Salicylates disrupt respiration and metabolism. In severe toxicity, acute lung injury may occur. However, the most important effect is on the mitochondria. Salicylates uncouple

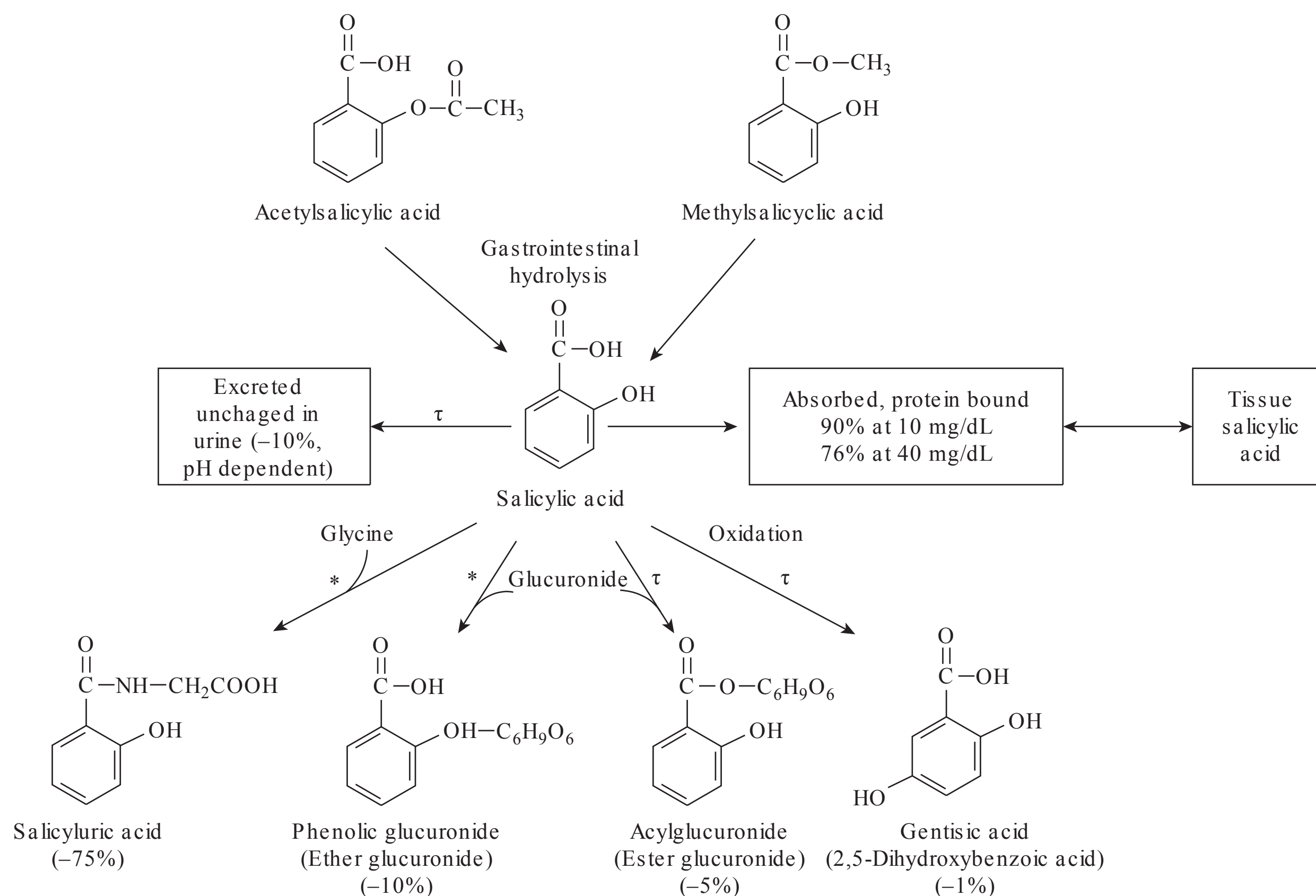


FIGURE 52-1 Salicylate metabolism. (Reproduced with permission from Goldfrank LR, Nelson LS, Howland MA, et al: *Salicylates in Goldfrank's Toxicological Emergencies*, 8th edition. New York: McGraw-Hill Companies Inc; 2006.)

oxidative phosphorylation, which means the energy generated from the electronic transport chain is dissipated as heat and not available for ATP formation. Heat generation manifests as hyperthermia, and lack of ATP for cellular energy leads to increased anaerobic metabolism and production of pyruvate

and lactic acid.⁹ Lipid metabolism is also stimulated, leading to generation of ketones and anion gap acidosis.¹⁰ Salicylates also inhibit ATP-dependent reactions resulting in increased oxygen consumption and carbon dioxide production. The increased lipid and glycogen metabolism is especially important in those with poor glycogen storage, for example, infants and chronic alcoholics.

Prior to alkalinization

Tissues pH 6.8	Plasma pH 7.1	Urine pH 6.5
HA ↓↑ H ⁺ + A ⁻	HA ↓↑ H ⁺ + A ⁻	HA ↓↑ H ⁺ + A ⁻

After alkalinization

Tissues pH 6.8	Plasma pH 7.4	Urine pH 8.0
HA ↓↑ H ⁺ + A ⁻	HA ↓↑ H ⁺ + A ⁻	HA ↓↑ H ⁺ + A ⁻

FIGURE 52-2 Alkalinization shifts equilibrium toward the plasma and urine and away from the tissues. (Reproduced with permission from Goldfrank LR, Nelson LS, Howland MA, et al: *Salicylates in Goldfrank's Toxicological Emergencies*, 8th edition. New York: McGraw-Hill Companies Inc; 2006.)

HISTORY

A careful history should be taken to the amount of salicylate the patient ingested and the presence of coingestants. The clinician should identify comorbid conditions that might complicate treatment, such as a history of liver disease, renal failure, or congestive heart failure. The chronicity of ingestion is vital when determining therapy. Acute overdoses are more likely in young patients and intentional overdoses. Ingestions of > 300 mg/kg is considered serious whereas > 500 mg/kg can be potentially fatal. Chronic toxicity is more likely in the elderly and from unintentional overuse. In contrast with acute ingestion, which is usually easily identified by history, chronic ingestion may not be apparent in the history. In some cases, patients have been hospitalized for days before chronic salicylate poisoning is identified.¹¹⁻¹³ The mortality rate for acute overdoses is about 1% compared with 25% for chronic toxicities.



TABLE 52-1: Salicylate Overdose Symptoms

Organ System	Minor/Moderate Symptoms	Severe Symptoms
Neurologic	Anxiety, difficulty concentrating, hallucinations, vertigo, lethargy, tremors, delirium	Seizures, coma, cerebral edema
Cardiovascular	Tachycardia	Hypotension, dysrhythmias, asystole
Pulmonary	Tachypnea (from stimulation of respiratory center), hyperpnea	Noncardiogenic pulmonary edema, respiratory arrest, apnea
Gastrointestinal	Nausea, vomiting (from stimulation of chemoreceptor in brain), abdominal pain (many focused on epigastric region), delayed gastric emptying	GI bleed, bowel perforation
ENT	Tinnitus	Deafness
Psychiatric	Exacerbation of underlying psychiatric illness	
Hematologic	Inhibition of platelet function and disturbances in clotting factors	
Metabolic	Hyperthermia, hypoglycemia, hyperglycemia	

CLINICAL MANIFESTATIONS

As expected, salicylate toxicity can present with various clinical findings (see Table 52-1). Patients can report anxiety, difficulty with concentration, hallucinations, lethargy, or even, at the end of the spectrum, with coma and seizures. On physical examination, patients may be tachycardiac, tachypneic, hyperpneic, and hyperthermic. In acute ingestions, nausea and vomiting may be prominent.

DIAGNOSTIC TESTING

Traditionally, a serum salicylate concentration of up to 30 mg/dL is considered therapeutic. Tinnitus, an early sign of toxicity, occurs at about 35 mg/dL. However, salicylate concentrations should be interpreted in context of the chronicity of ingestion. In acute toxicity, there is a large amount of salicylate in the GI tract and blood and proportionally less in the tissues. In contrast, in chronic salicylate poisoning, in which there is a high tissue burden, patients may exhibit toxicity at lower serum salicylate concentrations. Serum salicylate concentration may not correlate with the CSF salicylate concentration, which is why clinical symptoms are more important than serum concentrations. A toxicity nomogram was once proposed for salicylate poisoning but is not recommended because it does not accurately predict poisoning.¹⁴

A normal anion gap does not exclude salicylate poisoning. In some analyzers, the anion gap may be falsely normal if the presence of salicylate ions errantly elevates the reported chloride concentration.^{15–17} Salicylate poisoning causes both primary metabolic acidosis and primary respiratory alkalosis. Respiratory alkalosis predominates early in poisoning. As toxicity worsens, a metabolic acidosis develops. Pure metabolic acidosis is unusual in adults unless combined with coingestions of respiratory depressants. Serum pH of ≤ 7.4 in salicylate poisoning is a marker of severe toxicity.

Electrolyte and fluid abnormalities may occur in salicylate toxicity as a result of both poisoning and therapy. Emesis

and diaphoresis can cause severe hypovolemia. Hypokalemia can result from vomiting and therapeutic alkalinization, and serum calcium levels may drop from alkalinization. In severe salicylate poisonings, serum glucose concentration can be high from glycogenolysis and gluconeogenesis in the earlier stages and low from impaired gluconeogenesis and increased usage in later stages. However, be mindful that salicylate toxicity can decrease CNS glucose concentration despite a normal peripheral glucose concentration.¹⁸

MANAGEMENT

As with most emergency critical care, the clinician should ensure that the airway is stable. However, intubation in a severe salicylate overdose can be dangerous. The presence of hyperpnea and tachypnea should not necessarily be interpreted as “respiratory distress” requiring intubation. Rather, intubation and mechanical ventilation should be reserved for patients who are no longer protecting their airway, are failing to oxygenate, or have serum pH indicating that they are failing to maintain respiratory alkalosis. In severe poisonings, patients are dependent on tachypnea and hyperpnea to breathe off carbon dioxide and maintain near-normal pH. If ventilation is abruptly decreased, a sudden rise in carbon dioxide and drop in serum pH may occur, resulting in passage of more salicylate into the tissues and worsening poisoning. In a case series, mechanical ventilation was associated with worsening of pH in salicylate-poisoned patients.¹⁹

If intubation is necessary, an experienced operator should perform the procedure. To minimize hypoventilation, a rapid-onset sedative and paralytic should be used, and patients should be hyperventilated throughout until initiation of laryngoscopy. Once intubated, patients should be hyperventilated to maintain the respiratory alkalosis compensating for the metabolic acidosis. Patients should be sedated to prevent breath-stacking and ventilatory asynchrony. Paralytics may be necessary to facilitate ventilation. If patient is able

to initiate own breath, the CPAP mode of ventilation should be considered because it will allow the patient to breathe at his or her own rate. As the sedative and paralytic effects dissipate, the patient's tachypnea and hyperpnea may return and may cause "breath stacking" and ventilatory asynchrony. Frequent blood gases should be obtained and serum pH should be maintained between 7.5 and 7.6.

Gastric Decontamination and Activated Charcoal

Gastric lavage should be only considered if a dangerous amount of tablets is still in the stomach. This is usually only within 60 minutes of ingestion, so gastric lavage is rarely used. The risk of aspiration usually outweighs the benefits of possible extraction of tablets still in the stomach. If performed, lavage should be followed by activated charcoal.²⁰

Ipecac should not be used and was shown to be inferior to activated charcoal in lowering the absorption of salicylates.²¹

Activated charcoal should be administered in all patients who are not at risk of pulmonary aspiration. It reduces the absorption of therapeutic aspirin doses by 50–80%.²² Adding sorbital to activated charcoal may prevent salicylate absorption.²³ It is not clear whether there is increased benefit to multiple-dose activated charcoal.^{24–27} In theory, multiple-dose activated charcoal will decrease absorption of salicylate still present in the GI tract from bezoar formation or enteric-coated formulations. We recommend charcoal with sorbital on initial presentation followed by charcoal without sorbital at 4-hour intervals until salicylate poisoning has resolved.

Whole bowel irrigation (oral administration of polyethylene glycol electrolyte lavage solution) does not increase the clearance of absorbed salicylate.^{27,28}

Alkalinization

Since an increase in pH shifts the equilibrium of salicylate to the ionized state, alkalinization of blood will limit salicylates from entering other organs (most importantly the brain). This phenomenon has been described as "ion trapping" because ionized salicylate is trapped in the plasma and thus cannot pass into tissues. Serum alkalinization results in urine alkalinization, which may increase elimination by trapping ionized salicylate in the renal tubules. In support of this concept, it has been shown that elimination of salicylates is dependent on urinary pH.^{29,30} Excretion increases from 2% in acidic urine to 31% in alkaline urine. As expected, the half-life of salicylate also decreases and total body clearance of salicylate increases under alkaline conditions.³⁰

Alkalinization should be considered in patients with serum salicylate concentration > 35 mg/dL and suspected salicylate toxicity until blood pH is available to properly guide treatment. Alkalemia should be achieved with intravenous sodium bicarbonate. The goal should be plasma pH between 7.45 and 7.55 and urinary pH of 7.5–8.0. (We recommend adding 150 mEq of sodium bicarbonate to 1 L of

D5W and administering at 150–200 mL/h or twice maintenance rate.) In a critically ill patient receiving bicarbonate therapy, frequent serum and urinary pH should be obtained to determine bicarbonate dosage. Carbonic anhydrase inhibitors, which alkalinize urine, should not be used because they create a metabolic acidosis.

Potassium and calcium are important electrolytes to monitor in salicylate toxicities. Hypokalemia can result from induced alkalemia, urinary potassium loss, diarrhea if cathartic is used, and metabolic alkalosis from vomiting. In the presence of hypokalemia, alkalosis therapy may be hindered. Hypocalcemia can result from bicarbonate therapy and must be repleted quickly.

Extracorporeal Treatment

Extracorporeal treatment can be used to correct fluid, electrolyte, acid–base, and urea abnormalities along with clearing unwanted solute. In salicylate overdose, extracorporeal treatment is usually reserved for patients with severe toxicity or those who cannot tolerate conventional therapy. It is recommended for patients with CNS toxicity, acute lung injury or pulmonary edema, renal insufficiency, refractory acidosis, or clinical deterioration despite medical therapy. In the absence of these conditions, extracorporeal treatment should be performed for serum salicylate concentration > 100 or > 60 mg/dL in chronic poisonings (see Table 52-2).³¹ The serum salicylate concentration indication for extracorporeal treatment in chronic ingestions is set lower, since many cases of fatal cases report lower serum concentrations, some in the 50- to 70-mg/dL range.³² A patient on mechanical ventilation should also be considered, since mechanical ventilation alone may be inadequate to maintain respiratory alkalosis. Finally, hepatic dysfunction may require extracorporeal treatment as salicylates are metabolized by the liver.

Hemodialysis is the extracorporeal technique of choice. Hemoperfusion provides better clearance but hemodialysis has the added benefit of correcting electrolyte imbalances and acid–base disorders. Hemodialysis and hemoperfusion can be done in series but this method is rarely used in reality.³³ In hemodynamically unstable patients who cannot tolerate large



TABLE 52-2: Indications for Extracorporeal Treatment in Salicylate Overdose

- CNS disturbances: altered mental status, seizures, coma, cerebral edema
- Renal insufficiency
- Refractory serum acidosis despite aggressive medical therapy
- Clinical deterioration despite aggressive medical therapy
- Plasma salicylate concentration > 100 mg/dL (7.2 mmol/L) in acute ingestions or > 60 mg/dL (4.3 mmol/L) in chronic ingestions (some clinicians set concentrations lower, especially for chronic ingestions)
- Consideration for mechanically ventilated patients with hepatic dysfunction

fluid shifts caused by hemodialysis, continuous venovenous hemodiafiltration can be used.³⁴ Extracorporeal treatments should be used in conjunction with other therapies, and other therapies should not be held while waiting for extracorporeal treatment.

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ULTRASONOGRAPHY IN CRITICAL CARE

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Point-of-Care Echocardiography in the Emergency Department

Sasha K. Shillcutt • Daniel W. Johnson • Enyo A. Ablordeppey

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OVERVIEW

Point-of-care echocardiography is ideally suited to the care of the critical patient in the emergency department (ED), intensive care unit (ICU), or perioperative arena. It is highly accurate, noninvasive, portable, rapidly performed, easily repeatable, and simple to learn. It can provide critical information in real time in the setting of life-threatening emergencies. Point-of-care echocardiography increases patient safety, improves diagnostic accuracy, reduces diagnostic uncertainty, improves efficiency, and saves lives.

The purpose of this chapter is to provide a general understanding of point-of-care echocardiography as it is applied and accepted in the ED and ICU setting. We present an overview of how echocardiography can be utilized in the management of the critically ill patient. This chapter is not intended as a complete reference, and it assumes a basic understanding of ultrasound physics, image generation, ultrasound modes, terminology, and system operation.

SCOPE OF PRACTICE

Point-of-care ultrasound developed originally in Japan and Europe and came into emergency medicine practice in United States in the 1990s. Point-of-care echocardiography is considered core content of the specialty of emergency medicine by the American Board of Emergency Medicine.¹ The American Medical Association supports the use of ultrasound

by appropriately trained clinicians in varied specialties and supports specialty-specific guidelines for training, education, and oversight.²

Point-of-care echocardiography is not the same as a comprehensive echocardiogram or an ultrasound study done in a traditional imaging suite. It is performed, interpreted, and integrated into patient care in real time at the bedside. The goal is to immediately impact patient care by quickly and accurately performing a brief or focused exam designed to answer simple yes and no questions. The exam should focus on immediate life-threatening conditions and assess response to resuscitative measures. Point-of-care echocardiography has evolved over the past two decades into a bedside diagnostic tool, a method to safety guide invasive procedures, and a way to noninvasively assess and monitor ongoing resuscitation. The most current *American College of Emergency Physicians (ACEP) Emergency Ultrasound Guidelines* provide a comprehensive overview of the scope of practice, and training and credentialing guidelines, and these guidelines serve as an excellent reference for any department starting and developing a point-of-care ultrasound program.³ In 2010, the ACEP along with the American Society of Echocardiography (ASE) published a consensus statement on the use of ultrasound in the emergent setting.⁴ These recommendations, along with recent Focused Ultrasound Recommendations published by the ASE in 2013 for the use of ultrasound for critically ill patients, demonstrate the importance of clinical ultrasound in the hands of acute care physicians.⁵

ECHOCARDIOGRAPHY: CLINICAL INDICATIONS

Echocardiography is an essential skill for emergency medicine physicians and is especially well suited to the critically ill patient. Using simple qualitative echocardiography, emergency medicine physicians can rapidly and definitively assess for cardiac activity in cardiac arrest, evaluate for pericardial effusion and tamponade, estimate left ventricular (LV) systolic function, noninvasively estimate preload and right ventricular (RV) filling pressure, identify acute right heart strain, direct resuscitation and medical decision making, and immediately differentiate treatable causes of pulseless electrical activity (PEA) and shock. This chapter will focus on image acquisition, image interpretation, and integration of this information obtained into the care of the critically ill patient.

ECHOCARDIOGRAPHY: TECHNICAL CONSIDERATIONS

Echocardiography is a technically challenging study to perform for many reasons. The heart is surrounded by the ribs and sternum as well as the air-filled lungs that expand and compress with a varying respiratory rate. Both of these impede image acquisition by reflecting and scattering the sound waves, respectively. In addition, differences in body habitus, particularly obesity and deformities of the chest wall, and chronic disease conditions, such as emphysema, may make performing an echocardiogram more difficult. The left lateral decubitus position is preferred for obtaining high-quality images, but many critical patients cannot be optimally positioned. Despite these inherent challenges, echocardiography rapidly provides critical, high-yield information, making it an invaluable tool.

The heart sits inside the left chest cavity at an oblique angle with the long axis of the heart running along a plane from the right shoulder to the left hip. The great vessels and base of the heart are cephalad and the apex is caudad. The right side of the heart is anteriorly and inferiorly located, while the left side of the heart is positioned in a more posterior and superior orientation. Knowing the basic anatomy and orientation of cardiac structures in the chest cavity will improve image acquisition and help to explain orientation of structures.

The phased array transducer is the transducer of choice for echocardiography (Figure 53-1). Its small footprint and wide field of view allow easy manipulation and imaging between intercostal spaces. Temporal resolution (frame rate) is important in the dynamic imaging of echocardiography.

Standard cardiac orientation orients the image toward the patient's head or left side, with the image indicator appearing in the upper right of the ultrasound screen. Views will be obtained with the transducer indicator oriented to the patient's head or left side. This leftward orientation is the opposite of abdominal sonography, in which the image is oriented toward the patient's head or right side. Most ultrasound systems have a cardiac or echo preset that will automatically orient the image. The techniques and images in this chapter are presented in the traditional leftward or cardiac orientation.

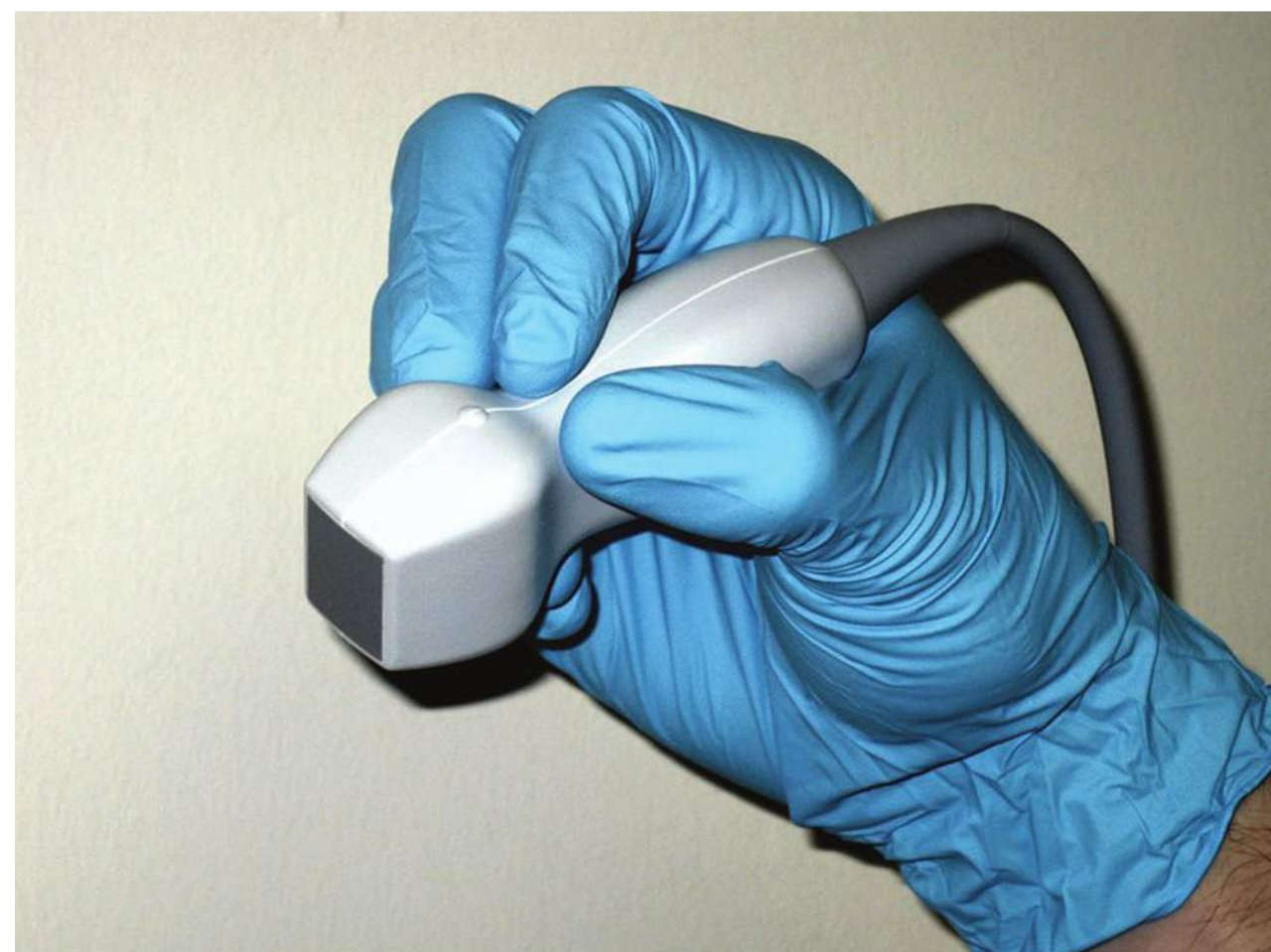


FIGURE 53-1 Phased array transducer. Its small footprint and superior frame rate make it the transducer of choice for echocardiography.

It is important to remember that surface echocardiography, or transthoracic echocardiography, images the cardiac structures from an anterior to posterior anatomic position.

Echocardiography is a dynamic medium, and still images do not convey the same amount of detail and information as live imaging. Most modern ultrasound systems have the capability to store digital video clips, which is the preferred image storage modality.

ECHOCARDIOGRAPHY: IMAGING WINDOWS AND VIEWS

Many imaging windows and views have been described in echocardiography. We present a series of five views that allow for a rapid and comprehensive evaluation. These include the subxiphoid four-chamber view, subxiphoid longitudinal inferior vena cava (IVC) view, parasternal long-axis view, parasternal short-axis view (both at the aortic valve level and the LV level), and apical four-chamber view. Additional views, such as the apical five-chamber view, will be discussed when evaluating LV systolic function. The authors recommend obtaining as many views as possible on each patient. Each view has strengths and weaknesses, and additional views may add additional critical information. One view may be sufficient in certain settings, such as cardiac arrest, but generally five views allow for a more accurate and comprehensive assessment. An overview of the windows and views that will be discussed and the structures displayed in each view are listed in Table 53-1.

Subcostal Four-Chamber View

To obtain the subxiphoid four-chamber view, place the transducer in the subxiphoid region, point the transducer indicator toward patient's left side, and aim the ultrasound beam toward patient's left shoulder at a shallow angle (Figure 53-2). Identify the liver, cardiac silhouette, right ventricle, left ventricle,



TABLE 53-1: Surface Echocardiography Windows and Views

Window	View	Anatomic Structures Evaluated
Subcostal	Four-Chamber	Right and left ventricle, intraatrial and intraventricular septum, tricuspid valve, mitral valve
Subcostal	RA/IVC View	IVC/hepatic veins collapsibility, “sniff test”
Parasternal	Long-Axis	Aortic valve, ascending aorta, LV outflow tract, anteroseptal & inferolateral walls, mitral valve
Parasternal	Short-Axis (AV level)	Right atrium, right ventricle, tricuspid valve, pulmonic valve, pulmonary artery, aortic valve, TAPSE
Parasternal	Short-Axis (LV level)	Thickening of all 6 walls of LV, filling of LV
Apical	Four-Chamber	Atria, right and left ventricle, intra-atrial and intraventricular septum, tricuspid valve, mitral valve, pulmonary veins

RA, right atrium; IVC, inferior vena cava; AV, aortic valve; LV, left ventricle; TAPSE, tricuspid annulus planar systolic excursion.

right atrium, left atrium, and pericardial space (Figure 53-3). Adjust the image by tilting, rocking, rotating, or sliding the transducer to align the beam angle so that all structures are in view.

This view is the easiest four-chamber view to obtain and provides a great global overview of all four cardiac chambers. It allows for evaluation of pericardial effusion and evaluation of chamber size. This view is best during cardiopulmonary resuscitation because it does not interfere with resuscitative efforts including chest compressions, central lines, and pacer pads. This is generally the easiest view to obtain in patients with emphysema or other chest deformities.

Common mistakes when performing this view include too steep an angle of the ultrasound beam, as well as not enough depth to visualize the entire heart. A tip to allow a shallow angle of approach is to grasp the transducer from above, which allows a shallower angle without the operator’s hand in the way. Stomach gas may obscure this view, which may be improved with either steady transducer pressure or having the patient take and hold a deep breath. Becoming familiar with

the various troubleshooting techniques will allow for more efficient imaging.

Subxiphoid Right Atrium/Inferior Vena Cava (RA/IVC) View

To obtain the subxiphoid RA/IVC view, place the transducer in the subxiphoid region, point the transducer indicator toward patient’s head, and sweep into the patient’s right upper quadrant to find the IVC running through the liver in a longitudinal plane (Figure 53-4). Identify the liver, the IVC running through the liver, the junction of the IVC and hepatic veins, the junction of the IVC and right atrium, the right atrium, the RV, and the pericardial space (Figure 53-5). Adjust the image by tilting, rocking, rotating, or sliding the transducer to align the beam angle so that all structures are in view. The IVC may also be imaged in cross-section, but the longitudinal view is the authors’ preference.

This view allows noninvasive assessment of central venous pressure (CVP) during normal respiration, using both IVC



FIGURE 53-2 Subxiphoid four-chamber probe placement. Proper probe positioning for the subxiphoid four-chamber view is with the transducer below the xiphoid process in the epigastrium, pointing toward the left shoulder at a shallow angle, while the transducer indicator faces the patient’s left side.



FIGURE 53-3 Subxiphoid four-chamber view of a normal heart. Note the right ventricle and right atrium in the near field and the larger left ventricle and atrium in the far field. The bright echogenic pericardium can be seen wrapping from the right atrium around the apex to the left atrium.



FIGURE 53-4 Subxiphoid inferior vena cava (IVC) probe placement. Proper probe positioning for the subxiphoid IVC view is with the transducer below the xiphoid process, angled slightly upward, while the transducer indicator faces the patient's head. Once in this position, sweep laterally into the right upper quadrant until the IVC can be seen running through the liver into the right atrium. Alternatively, this view can be achieved by obtaining a subxiphoid four-chamber view with the right atrium in the center of the screen and then rotating the transducer 90 degrees counterclockwise.

diameter and respiratory change. M-mode is useful to obtain both maximal and minimal diameters of the IVC during the respiratory cycle (Figure 53-6).

A common mistake when performing the subxiphoid longitudinal IVC view is failing to tilt the transducer to reduce the angle of the ultrasound beam. When measuring the IVC diameter, it is important to have the long axis of the IVC perpendicular to the ultrasound beam. In addition, the IVC and abdominal aorta may be confused. The IVC is more



FIGURE 53-5 Subxiphoid inferior vena cava (IVC) view of a healthy subject. Note the IVC is seen running through the liver, with thin walls, and joining the right atrium. Within the liver, the hepatic vein can be seen emptying into the IVC. The proper location for measuring IVC diameter is just distal to this junction.

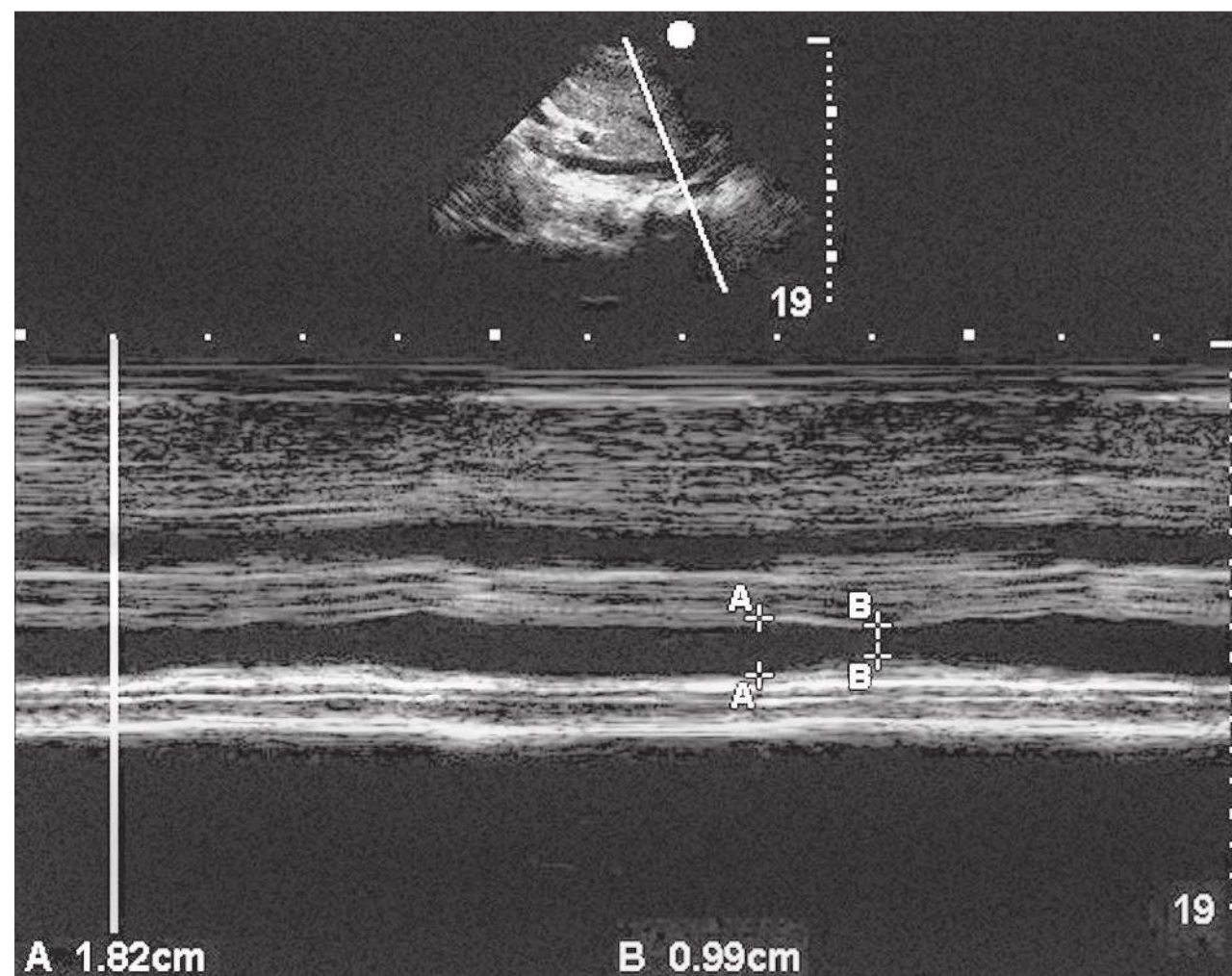


FIGURE 53-6 Subxiphoid inferior vena cava (IVC) M-mode view showing normal IVC diameter (1.5–2.5 cm) with normal respiratory collapse (~50%).

to the patient's right, runs through the liver, has thin walls, generally exhibits respiratory variation, and enters the right atrium. The aorta is more to the patient's left, runs posterior to the liver, has thick echogenic walls, and has the celiac and superior mesenteric artery vessels exiting anteriorly.

Parasternal Long-Axis View

To obtain the parasternal long-axis view, place the transducer perpendicular to chest wall in the left fourth to sixth parasternal space, and point the transducer indicator toward patient's right shoulder (Figure 53-7). Identify the right ventricle, left ventricle, left atrium, mitral valve, aortic valve, aortic root,



FIGURE 53-7 Parasternal long-axis probe placement. Proper probe positioning for the parasternal long-axis view is with the transducer in the fourth to sixth intercostal space immediately to the left of the sternum, while the transducer indicator is pointing toward the patient's right shoulder.

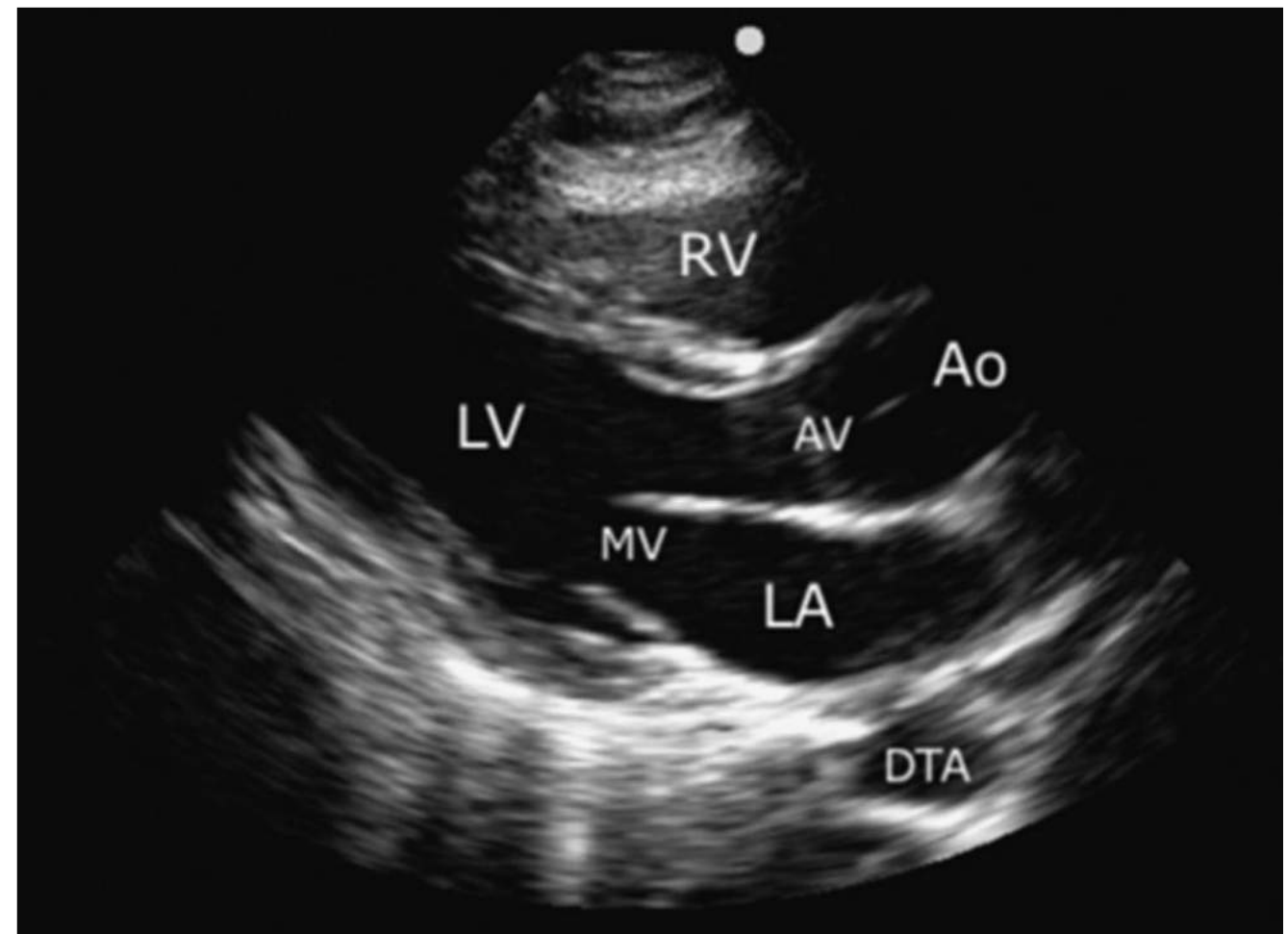
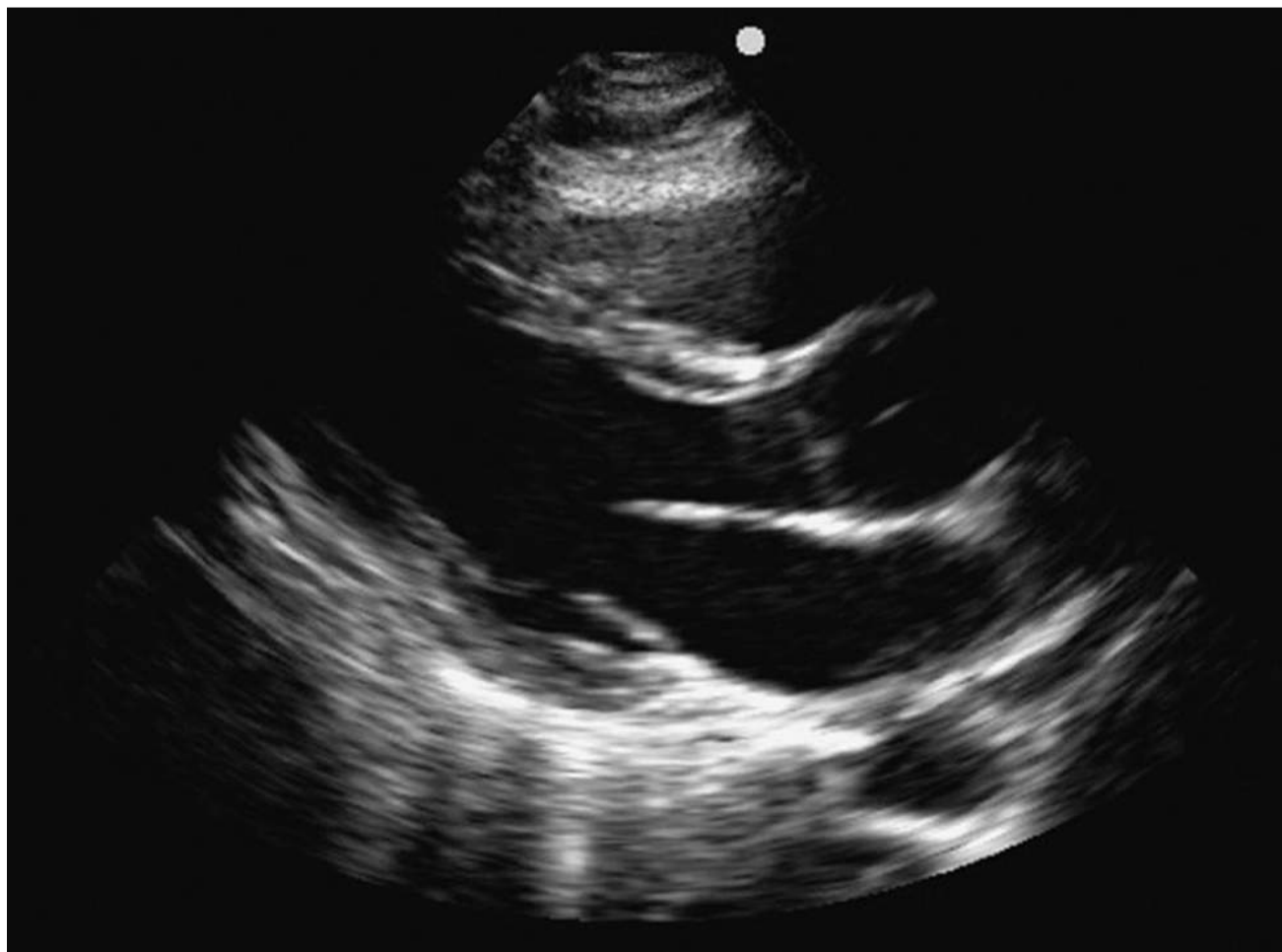


FIGURE 53-8 Parasternal long-axis view of a normal heart. The right ventricle (RV) is the most anterior chamber and the right atrium is not in view. A true long-axis view of the left ventricle displays both the aortic and mitral valves simultaneously. The mitral valve is open; the heart is in mid-diastole. Note the descending aorta posterior to the left ventricle. Just anterior to the aorta, the bright echogenic pericardium wraps around the heart in a clockwise fashion.

and descending thoracic aorta posterior to the left atrium (Figure 53-8). Adjust the image by tilting, rocking, rotating, or sliding the transducer to align the beam angle so that all the structures are in view. Rolling the patient into the left lateral decubitus position may allow for better image quality.

This is the best view for measurement of aortic root diameter, which should be < 3.8 cm in diameter. In order to perform Doppler estimation of cardiac output, the LV outflow tract (LVOT) diameter (LVOT D) should be measured in this view. This is also an excellent view for estimation of LV systolic function using qualitative methods.

Parasternal Short-Axis View

To obtain the parasternal short-axis view, place the transducer perpendicular to the chest wall in the left fourth to sixth parasternal space and point the transducer indicator toward the patient's left shoulder (Figure 53-9). This view can also be obtained by rotating the transducer 90 degrees clockwise from the parasternal long-axis view. Identify the right ventricle, left ventricle, and papillary muscles indenting the LV (Figure 53-10). The papillary muscles serve as a landmark to make sure the section in view is through the LV and not the left atrium or aortic root. To obtain this view, the operator may have to tilt the transducer slightly downward, toward the patient's left hip, along the long axis of the heart. Rolling the patient into the left lateral decubitus position may allow for better image quality.

It is important to note that there are two different views in the short-axis, one at the level of the aortic valve and one at the level of the LV. Both can be obtained in the same window. The aortic valve level is obtained by scanning superior to the LV level. This is an excellent view for estimation of LV systolic function and the best view for identification of regional LV systolic dysfunction. Scanning of the aortic valve in the short-axis allows for qualitative assessment of the aortic valve.

Apical Four-Chamber View

To obtain the apical four-chamber view, place the transducer at the point of maximum impulse (PMI), point the transducer indicator toward the patient's left axilla, and aim the ultrasound beam toward patient's right shoulder at a shallow angle (Figure 53-11). Alternatively, the apical window can be found by finding the apex of the heart in the parasternal long-axis view toward the left of the screen. The transducer is moved over the apex in real time and then rotated toward the patient's left axilla and the beam angle flattened. This is the most challenging basic view to obtain,



FIGURE 53-9 Parasternal short-axis probe placement. Proper probe positioning for the parasternal short-axis view is with the transducer in the fourth to sixth intercostal space immediately to the left of the sternum, while the transducer indicator is pointing toward the left shoulder. Alternatively, this view can be achieved by obtaining a parasternal long-axis view and then rotating the transducer 90 degrees clockwise.

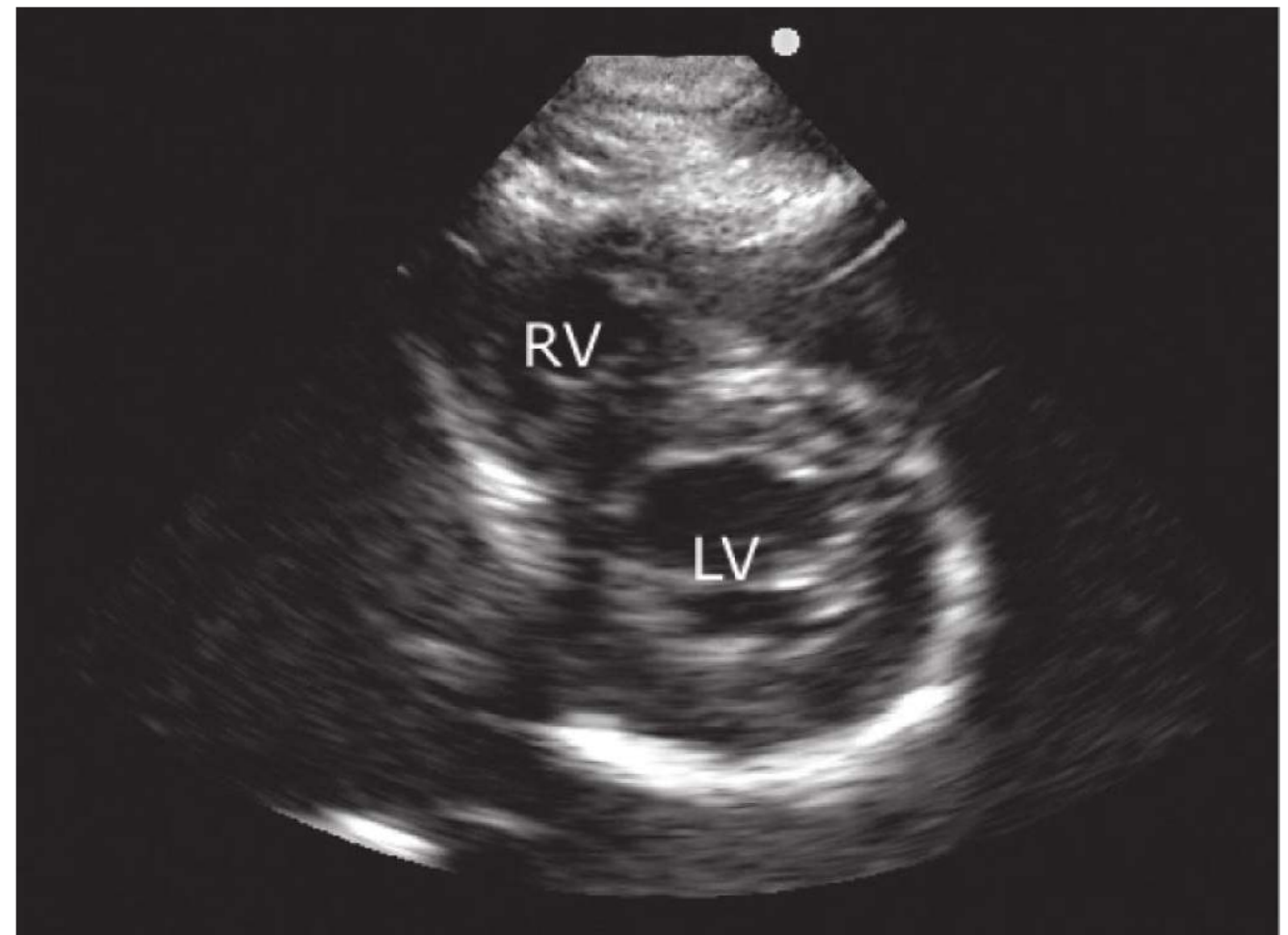


FIGURE 53-10 Parasternal short-axis view at the level of the papillary muscles of a normal heart. This marks the portion of the left ventricle immediately distal to the mitral valve, which is where left ventricular function is assessed. This view is also excellent for identifying regional wall motion abnormalities.

and rolling the patient into the left lateral decubitus position usually allows for better image quality. Identify the LV, mitral valve, left atrium, RV, tricuspid valve, and right atrium (Figure 53-12).

This is the best view for assessment of valvular pathology, as well as for comparing relative right and LV sizes. The normal right ventricle to left ventricle ratio is < 0.6 – 1 measured across valve leaflets. This view is also excellent for Doppler interrogation of inflow and outflow velocities for advanced echocardiographic hemodynamic applications.

TRAINING

One prospective study showed that a focused 6-hour training course significantly improved emergency medicine residents'

theoretical and practical knowledge of bedside echocardiography.⁶ The study enrolled 21 emergency medicine residents who underwent 5 hours of didactics and 1 hour of hands-on instruction on echocardiography. Subjects underwent preexposure and postexposure testing of their theoretical and practical knowledge. Practical scores significantly increased from 56% to 94%, and theoretical scores significantly improved from 54% to 76%. This study suggests that skills necessary for competent bedside echocardiography can quickly be learned and applied.

Current ACEP guidelines recommend performing at least 25 proctored exams prior to using bedside echocardiography independently in patient care decisions.³ The exception to this would be in a case where delaying treatment or further interventions in order to obtain some other reference standard would cause undue harm to the patient.

CLINICAL SCENARIOS

Echocardiography in Cardiac Arrest

Echocardiography can be a valuable tool in the setting of cardiac arrest. It enables the differentiation of organized and agonal cardiac contraction from cardiac standstill, providing prognostic information. In addition, it allows rapid diagnosis of potentially reversible causes of cardiac arrest, such as severe hypovolemia, tamponade, myocardial infarction, and acute right heart failure due to pulmonary embolus.

Three prospective observational studies have found 100% mortality for patients in cardiac standstill.^{7–9} A large, multicenter prospective observational trial is currently being conducted with a hypothesis that lack of cardiac activity on echocardiography predicts a mortality of 100%. The results of these studies have the potential to prevent futile resuscitative efforts. In addition to lack of myocardial activity, echocardiographic imaging during cardiac standstill may show



FIGURE 53-11 Apical four-chamber probe placement. Proper probe positioning for the apical four-chamber view is with the probe overlying the point of maximum impulse (PMI), pointing at a shallow angle toward the right shoulder, while aiming the transducer indicator toward the left axilla.

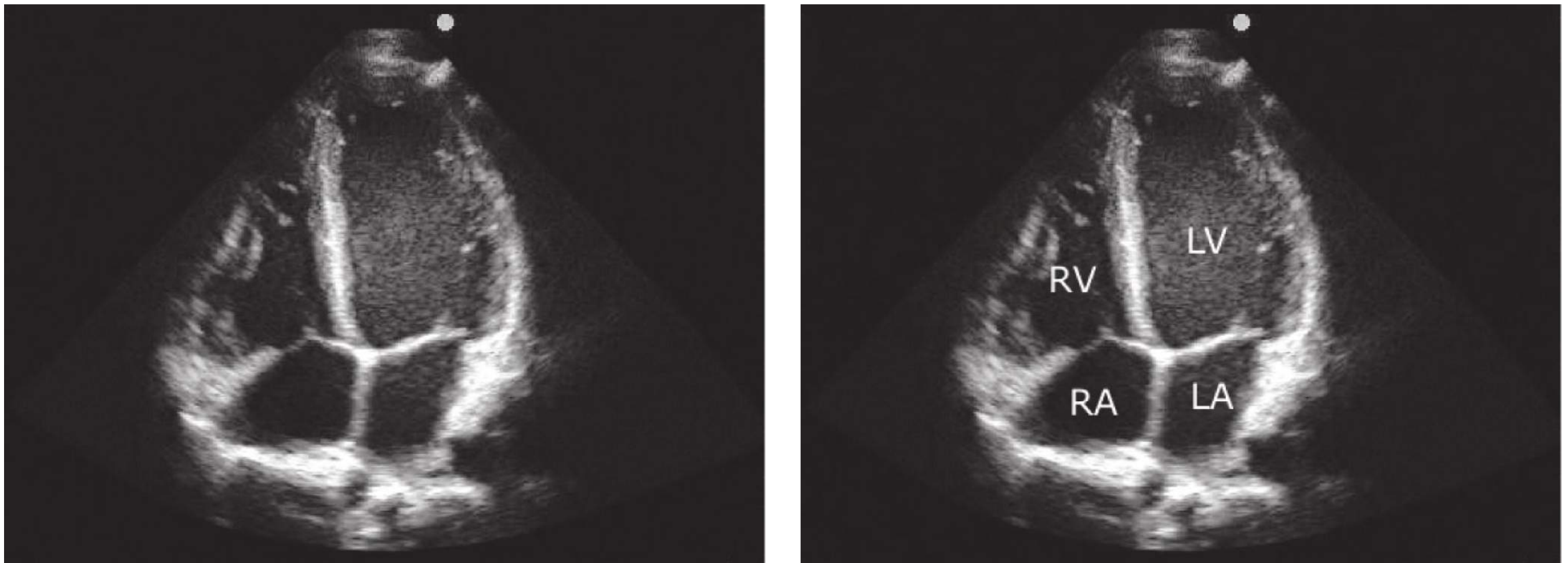


FIGURE 53-12 Apical four-chamber view of a normal heart. Note the normal right to left ventricular size ratio of $< 0.6:1$.

individual reflections from slow-moving red blood cells or blood clotting in the heart (Figure 53-13).

The presence of cardiac activity during any point of the resuscitative effort is strongly associated with survival to hospital admission. In a prospective observational trial of 102 patients in cardiac arrest, patients with cardiac activity at any point of the resuscitation survived at a much higher rate, 27% versus 3%.¹⁰ A similar study showed that 12 out of 18 patients (67%) with PEA and cardiac contractions survived to hospital admission.⁷ A third study showed that 8 out of 11 patients (73%) with PEA and cardiac contractions survived to hospital admission.⁸

Any cardiac motion corresponding with electrical impulses should be considered to be cardiac activity, and aggressive attempts at resuscitation should be continued. The presence of cardiac activity predicts return of spontaneous circulation.

Another benefit of point-of-care echocardiography during cardiac arrest is the ability to identify reversible causes, such as pericardial tamponade. In a prospective observational

study of 20 patients in cardiac arrest, the authors demonstrated pericardial effusions in 8 of 12 patients with cardiac motion, including 3 cases of tamponade.⁹ Finding a treatable cause of cardiac arrest, such as a large pericardial effusion, should prompt immediate definitive treatment. In this case, pericardiocentesis is indicated, preferably under ultrasound guidance. The findings of tamponade physiology are discussed later in the chapter.

A focused echocardiogram including parasternal long-axis, parasternal short-axis, apical, and subxiphoid views can be performed in less than 4 minutes by an experienced sonographer. In the setting of ongoing cardiac arrest, parts of this four-window exam can be completed during each pulse check, when compressions are halted. As previously mentioned, the subxiphoid four-chamber view is an excellent view during cardiac arrest. It does not interfere with chest compressions or other resuscitative efforts and provides an excellent global view of the heart. From this window, the heart can be quickly assessed for the presence of cardiac contraction, pericardial effusion and tamponade, and LV function, as well as RV size. Right ventricular dilation can be suggestive of pulmonary embolus, and a flat RV can be suggestive of severe hypovolemia. Chest compressions should not be halted in order to image the heart. Rather, the sonographer should seize opportunities to image the heart when access to a particular window is recognized.

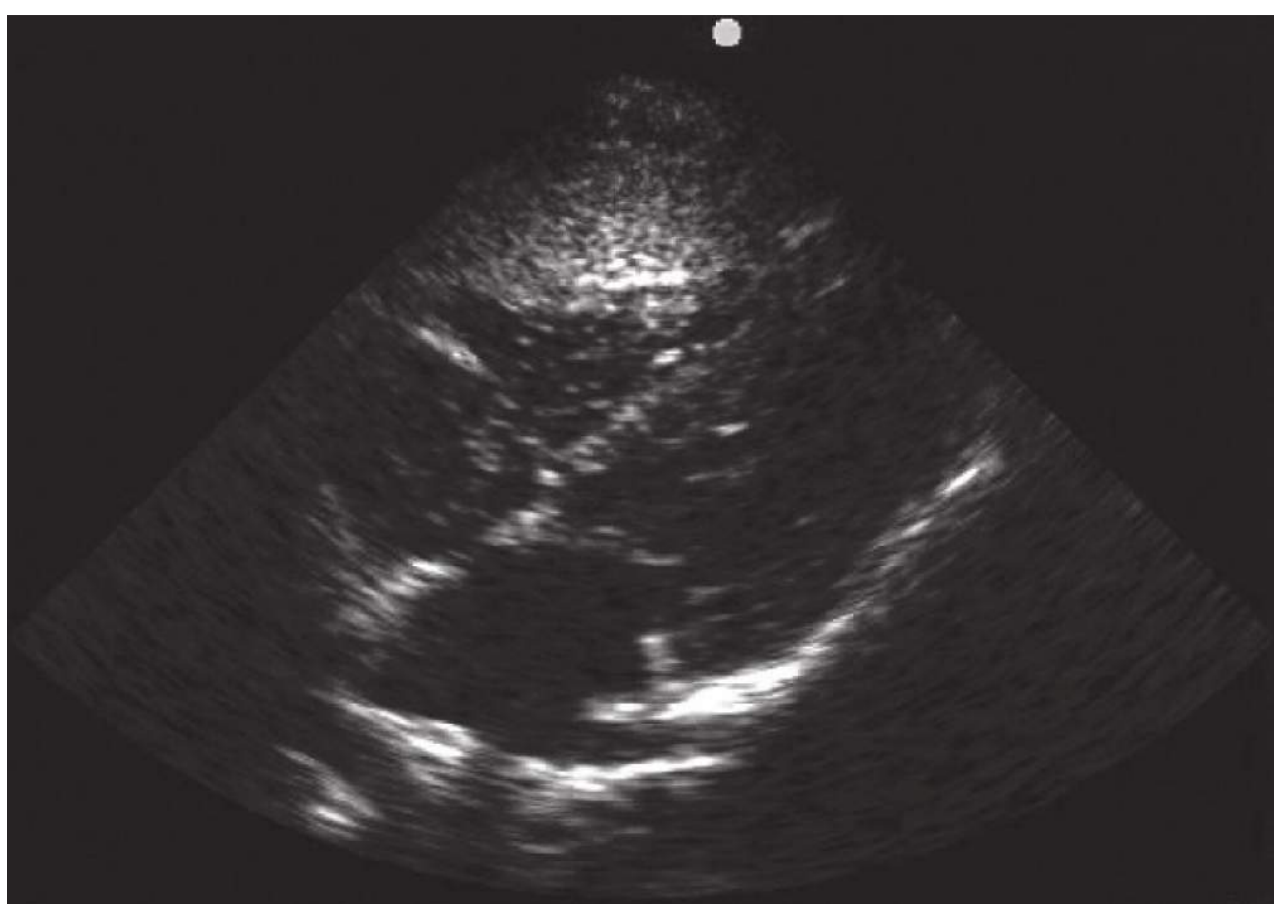


FIGURE 53-13 Subxiphoid four-chamber view in cardiac arrest with characteristic reflection of swirling, slow-moving red blood cells within the right atrium and ventricle.

Echocardiography to Identify Pericardial Effusion and Tamponade Physiology

Several studies have shown that emergency physicians can accurately identify pericardial effusion and tamponade physiology. One prospective observational study enrolled 515 patients at high risk for pericardial effusion and found 103 positive studies.¹¹ All studies were performed and interpreted by emergency physicians and subsequently reviewed by a cardiologist. Sensitivity and specificity of bedside echocardiography performed by emergency physicians for pericardial

effusion were 96% and 98%, respectively. Another study showed that patients with unexplained new-onset dyspnea may benefit from emergency physician–performed echocardiography to rule out pericardial effusion.¹² This prospective, observational trial enrolled 103 patients with new-onset dyspnea unexplained by pulmonary, infectious, hematologic, traumatic, psychiatric, cardiovascular, or neuromuscular disease after ED evaluation. Fourteen of 103 patients had effusions, with 4 classified as large.

In penetrating chest trauma, echocardiography has been shown to reduce time to diagnosis and decrease mortality. In one retrospective study, the authors reviewed the records of 49 patients with penetrating cardiac injury.¹³ Survival was 100% in the group with echocardiography, compared with 57% in the group without echocardiography. The average time to diagnosis and disposition for surgical intervention was significantly shorter at 15 minutes for the patients who received echocardiography versus 42 minutes for patients who did not receive echocardiography. A prospective multicenter study enrolled 261 patients, with 29 true positives confirmed in the operating room.¹⁴ Bedside echocardiography had a sensitivity of 100% and a specificity of 97% for the diagnosis of hemopericardium, and mean time from ED arrival to operative intervention in positive cases was 12 minutes. Due to its excellent test characteristics and time savings, the authors recommended bedside echocardiography as the initial diagnostic modality of choice in penetrating chest trauma.

A pericardial effusion appears as an anechoic fluid collection in the pericardial space. Effusions can be circumferential, but may be localized in postoperative patients, patients with inflammatory conditions, or very early in cardiac hemorrhage. Echogenic material may or may not be present within the effusion. The absence of significant pericardial effusion essentially rules out tamponade as a cause of hypotension.

Pericardial effusions are seen in many sizes. A small effusion may only be seen in the dependent portion of the pericardium and generally measures < 5 mm. Moderate pericardial



FIGURE 53-15 Subxiphoid inferior vena cava (IVC) view demonstrating a large pericardial effusion between liver and right atrium.

effusions are generally circumferential, and measure between 5 and 10 mm. Large pericardial effusions are circumferential and measure > 10 mm. Swinging of the heart in the pericardial sac may be seen and often manifests as electrical alternans on electrocardiography (Figures 53-14 to 53-18).

Pitfalls in diagnosing pericardial effusions do exist. The most common are mistaking a normal fat pad or pleural effusion for a pericardial effusion. These pitfalls can be avoided with careful scanning, observing the heart in multiple views, and identifying key landmarks.

A pericardial fat pad can often have a similar appearance to an effusion (Figure 53-19). Typically, a fat pad is only present anteriorly, has internal echoes, and moves with the heart. Using multiple views will allow the user to distinguish an anatomic fat pad from an abnormal pericardial effusion.

A left-sided pleural effusion is commonly mistaken for a pericardial effusion. Pericardial effusions are typically circumferential, whereas a pleural effusion is only seen posterior



FIGURE 53-14 Subxiphoid four-chamber view showing a moderate pericardial effusion with an anechoic fluid stripe circumferentially surrounding the heart.

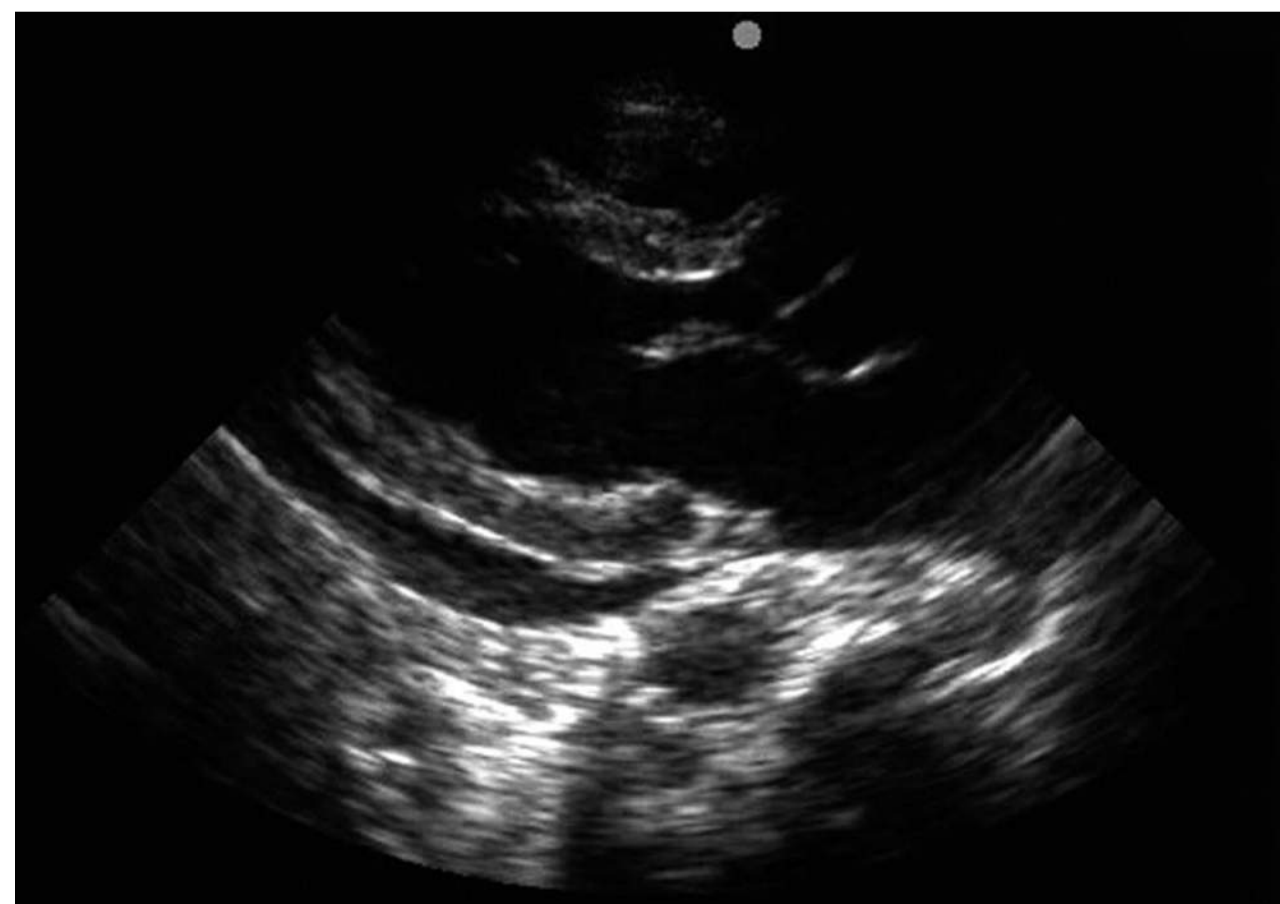


FIGURE 53-16 Parasternal long-axis view showing a moderate-sized pericardial effusion with an anechoic fluid stripe layering out posterior to the myocardium and anterior to the descending aorta.

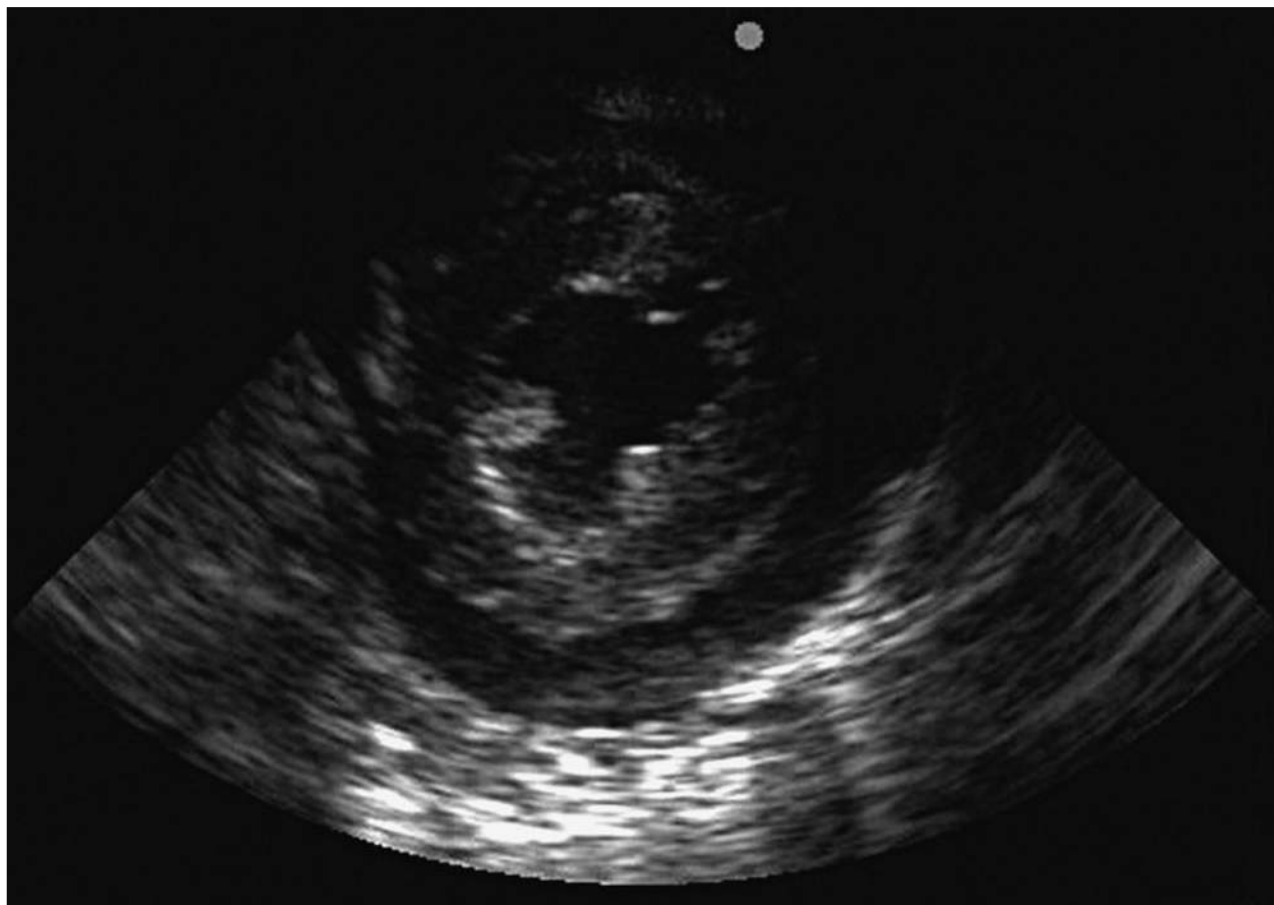


FIGURE 53-17 Parasternal, mid-papillary short-axis view of the left ventricle showing a large pericardial effusion with an anechoic fluid stripe circumferentially surrounding the heart.

to the heart. Key landmarks for identifying pericardial from pleural fluid are the left atrium and descending thoracic aorta on the parasternal long-axis view. Pericardial fluid will appear between the left atrium and descending aorta, whereas pleural effusion will be seen posterior to the descending aorta (Figure 53-20).

When a pericardial effusion is identified, tamponade must be considered. Tamponade is a time-critical clinical diagnosis of shock in the setting of a significant pericardial effusion. Increasing pressure in the non-distensible pericardium limits RV filling and venous return, leading to circulatory collapse. Tamponade is difficult to diagnose solely on clinical findings. A recent case series showed that pericardial tamponade can often present without the classic findings of Beck's triad and mimic more common disease processes.¹⁵

Qualitative echocardiography can show evidence of tamponade physiology. Findings consistent with tamponade physiology include collapse of the right atrium during systole,

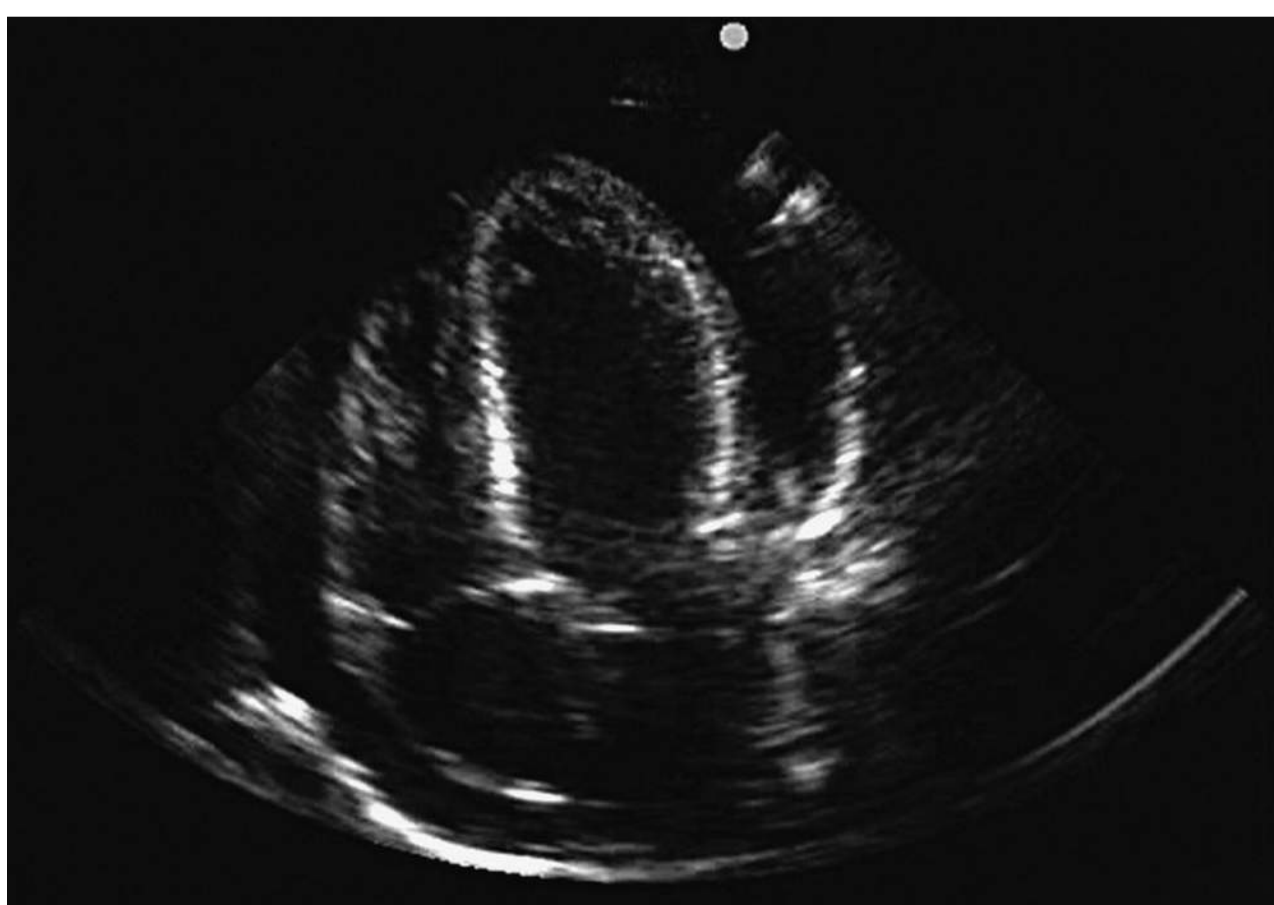


FIGURE 53-18 Apical four-chamber view showing a large pericardial effusion with an anechoic fluid stripe circumferentially surrounding the heart. Note the lack of right atrial or right ventricular collapse.

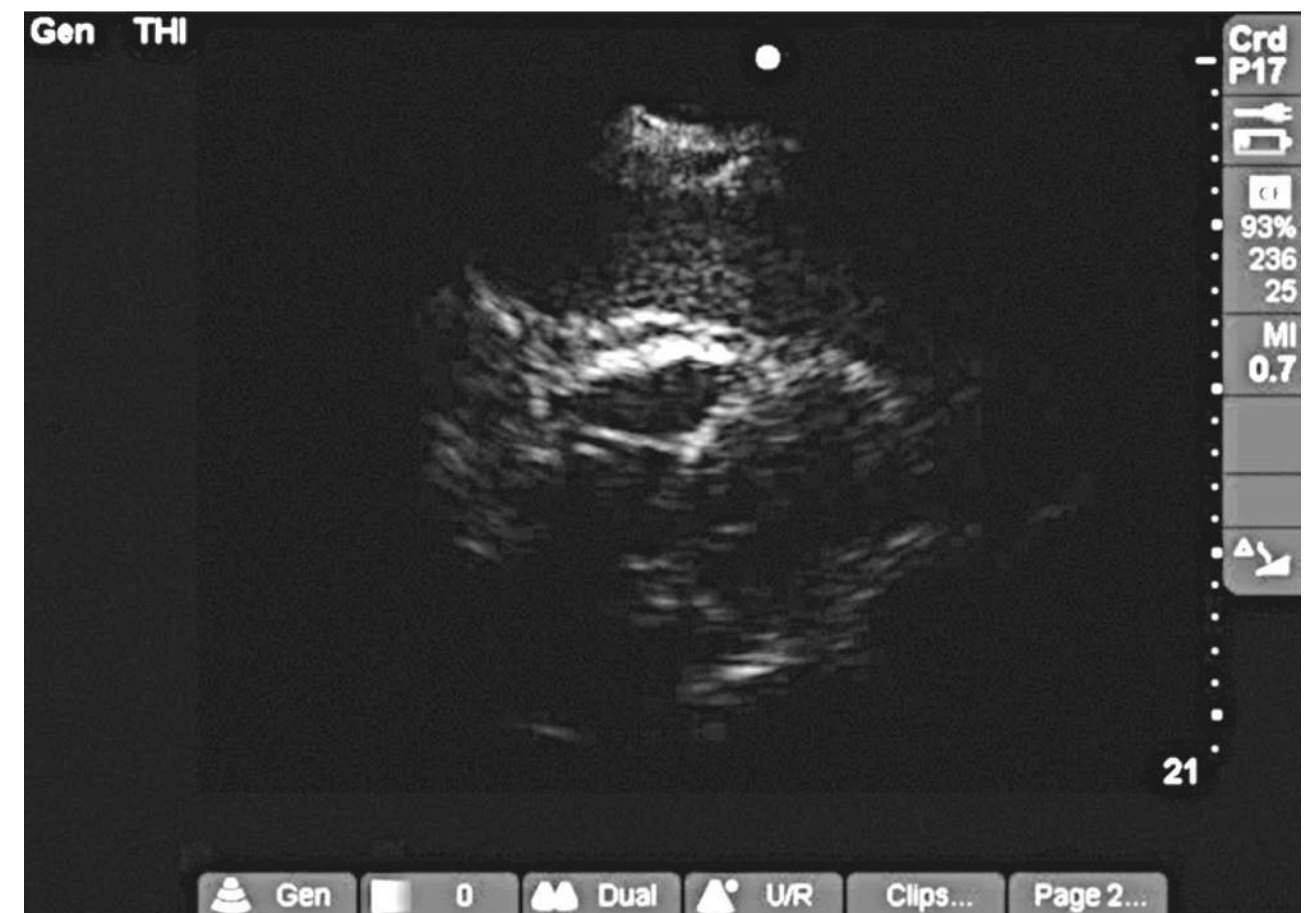


FIGURE 53-19 Subxiphoid four-chamber view showing a small pericardial fat pad anteriorly between the liver and right ventricle.

collapse of the RV during diastole, and dilation of the IVC with loss of normal respiratory variation (Figures 53-21 to 53-24).

Doppler echocardiography can also aid in the diagnosis of tamponade. Normal cardiac filling is influenced by respiratory phase, with LV filling reduced in inspiration. In tamponade, inspiratory filling impairment of the LV is exaggerated, which can be detected with pulsed wave spectral Doppler interrogation of mitral inflow velocities. This is best performed in the apical four-chamber view. The pulsed wave spectral Doppler gate is placed in the LV just distal to the tips of the mitral leaflets to measure mitral inflow velocity. Normal E-wave (early diastolic) velocity decreases with inspiration of < 10–15%. With tamponade, LV inflow is further restricted, leading to an exaggerated inspiratory decrease of > 25% in maximal E-wave velocity (Figure 53-25).¹⁶

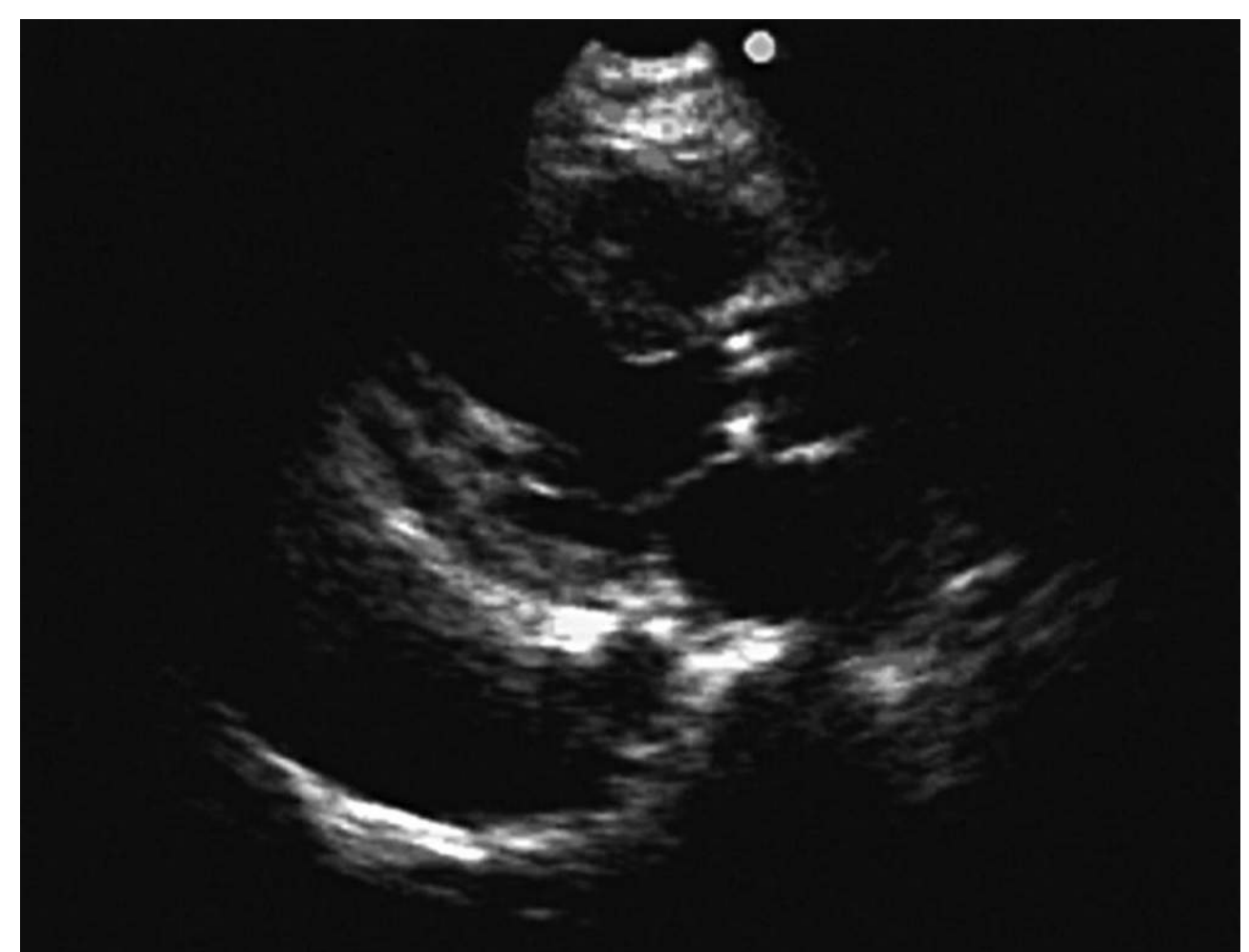


FIGURE 53-20 Parasternal long-axis view showing a large pleural effusion with an anechoic fluid stripe layering out posterior to the left ventricle and descending aorta. Compare this image with Figure 53-16 to see the difference between locations of a pericardial and pleural effusion.

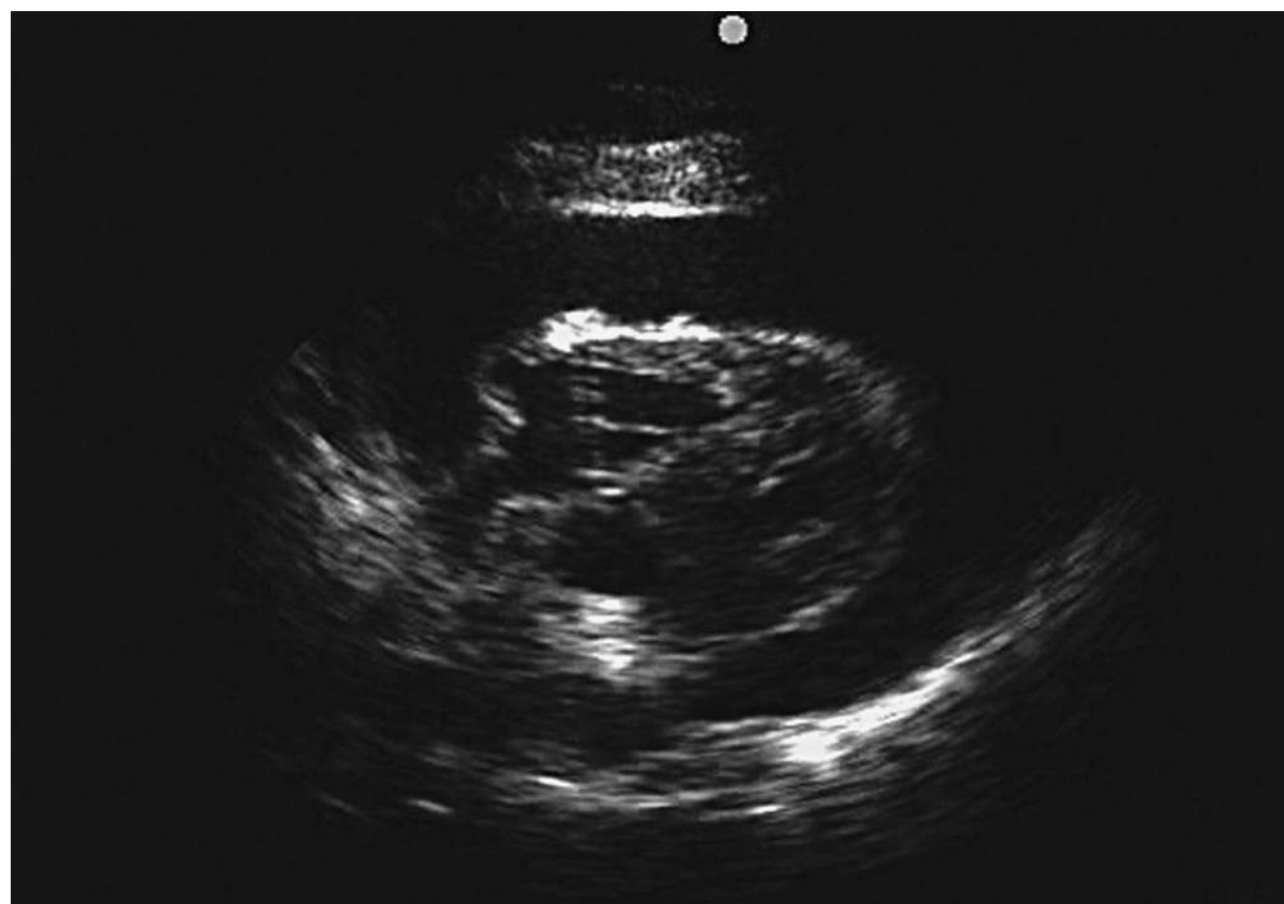


FIGURE 53-21 Subxiphoid four-chamber view showing right atrial collapse in the setting of a large circumferential pericardial effusion. The elevated pericardial pressure is causing right atrial collapse during systole, consistent with tamponade physiology.

A prospective observational study in 56 consecutive patients with pericardial effusion compared qualitative findings of tamponade and Doppler findings of tamponade.¹⁷ Sixteen patients were found to have tamponade and underwent drainage. A 22% decrease in peak mitral inflow velocity during inspiration had sensitivity of 77% and specificity of 80% for tamponade. Right ventricular collapse had sensitivity and specificity of 75% and 85%, respectively.

Echocardiography to Estimate Left Ventricular Systolic Function

Physicians can accurately estimate LV systolic function using point-of-care echocardiography. Both qualitative and quantitative estimation methods will be reviewed. Simple qualitative



FIGURE 53-23 Apical four-chamber view showing right atrial collapse in the setting of a circumferential pericardial effusion.

methods are fast, easy to learn, and correlate well with quantitative methods.

Several studies have shown that emergency physicians can accurately estimate LV systolic function. A prospective observational study enrolled 51 patients with symptomatic hypotension.¹⁸ Patients underwent bedside echocardiography by emergency physicians and were classified as having normal, depressed, or severely depressed ejection fraction. A blinded cardiologist interpreted these images and served as the gold standard, while a second cardiologist reviewed the studies to determine interobserver reliability between cardiologists. Pearson's correlation coefficient between emergency physician and cardiologist was 0.86, compared with 0.84 between the two cardiologists. Another prospective observational study enrolled 115 patients in whom emergency physicians performed bedside echocardiography and classified ejection fraction as poor, moderate, and normal.¹⁹

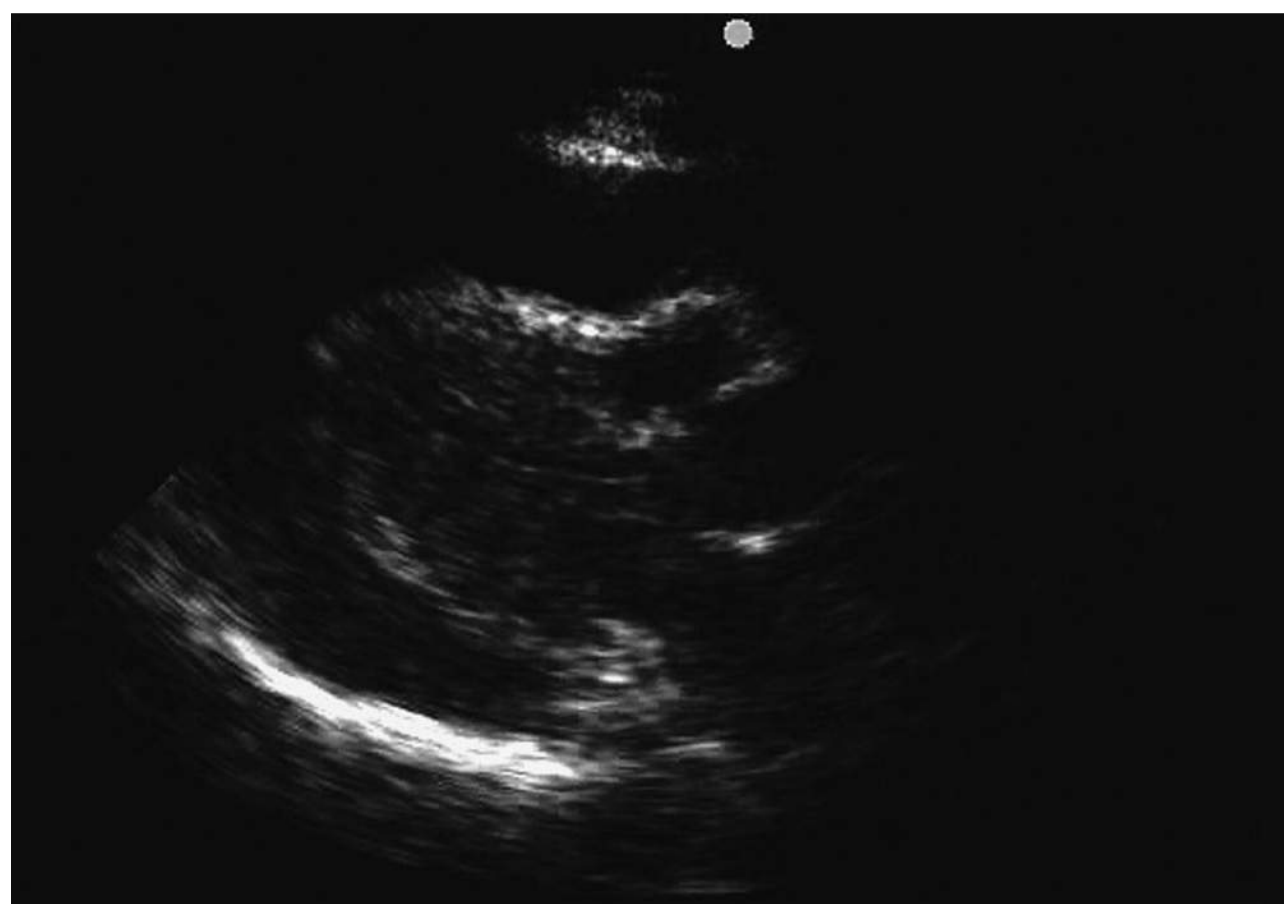


FIGURE 53-22 Parasternal long-axis view showing right ventricular collapse in the setting of a large pericardial effusion. The elevated pericardial pressure is causing right ventricular collapse during diastole, consistent with tamponade physiology.

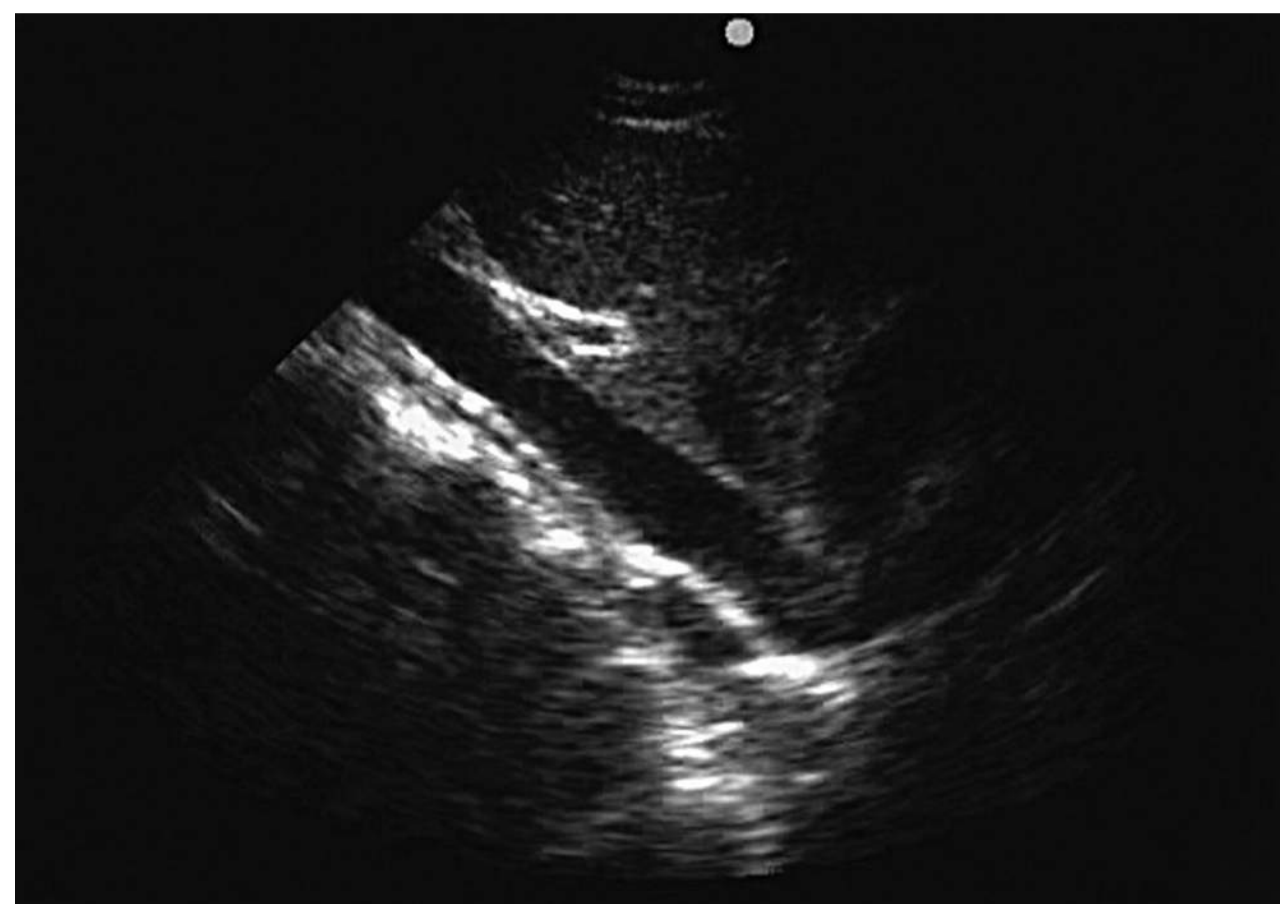


FIGURE 53-24 Subxiphoid inferior vena cava (IVC) view with pericardial effusion and dilated IVC. In tamponade, right atrial filling pressures are elevated, increasing IVC diameter and reducing respiratory variation in diameter.

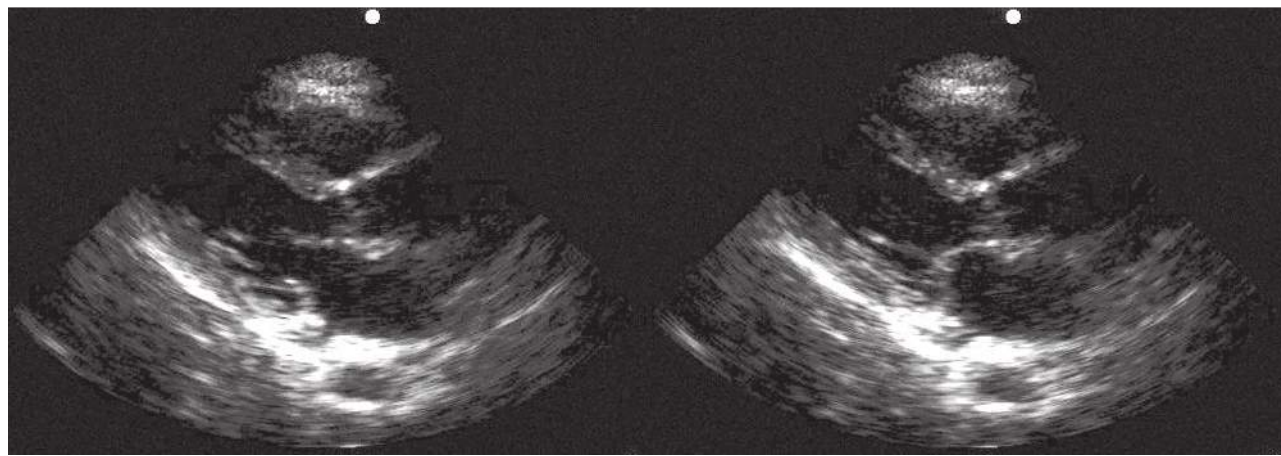


FIGURE 53-29 Parasternal long-axis view, depressed ejection fraction. Parasternal long-axis view during (a) diastole and (b) systole, demonstrating moderately reduced ventricular function. Note the incomplete excursion of the anterior mitral valve leaflet during diastole, < 40% reduction in left ventricular diameter during systole, and poor ventricular wall thickening during systole.

wide and fast, with the anterior leaflet almost touching the intraventricular septum (Figure 53-32). The distance between the anterior MV leaflet and septum at their closest point is known as the E-point septal separation (EPSS). When LV pressures remain high with poor LV function, the mitral valve opens more slowly and not as widely (Figure 53-33). The mitral valve can be assessed with M-mode, and this more accurately depicts mitral valve opening (Figures 53-34 and 53-35).

QUANTITATIVE ESTIMATION OF LEFT VENTRICULAR SYSTOLIC FUNCTION

Several methods exist to quantitatively measure LV systolic function. These methods can be time-consuming. Furthermore, qualitative estimation by an experienced sonographer has been shown to be as accurate as a measured quantitative estimation.

An estimated ejection fraction can be calculated using LV measurements obtained when measuring fractional shortening. Fractional shortening is determined by the following formula: $(\text{LV end-diastolic diameter} - \text{LV end-systolic diameter}) / \text{LV end-diastolic diameter}$. The normal range for fractional shortening is 30–45%. M-mode using either the parasternal long- or short-axis views can be used to accurately measure fractional shortening. Most ultrasound systems can calculate fractional shortening using built-in calculator packages from LV measurements. Fractional shortening can be used to

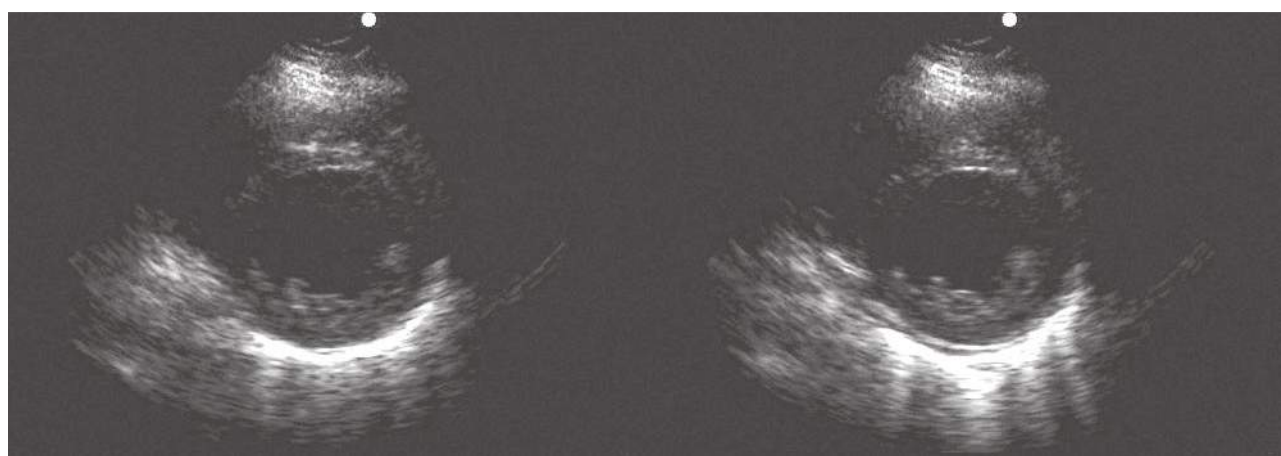


FIGURE 53-30 Parasternal short-axis view, dilated left ventricle (LV), poor ejection fraction. Parasternal short-axis view at the level of the papillary muscles showing poor LV systolic function. Note almost no change in LV cavity size or muscle wall thickness from (a) end diastole to (b) end systole.

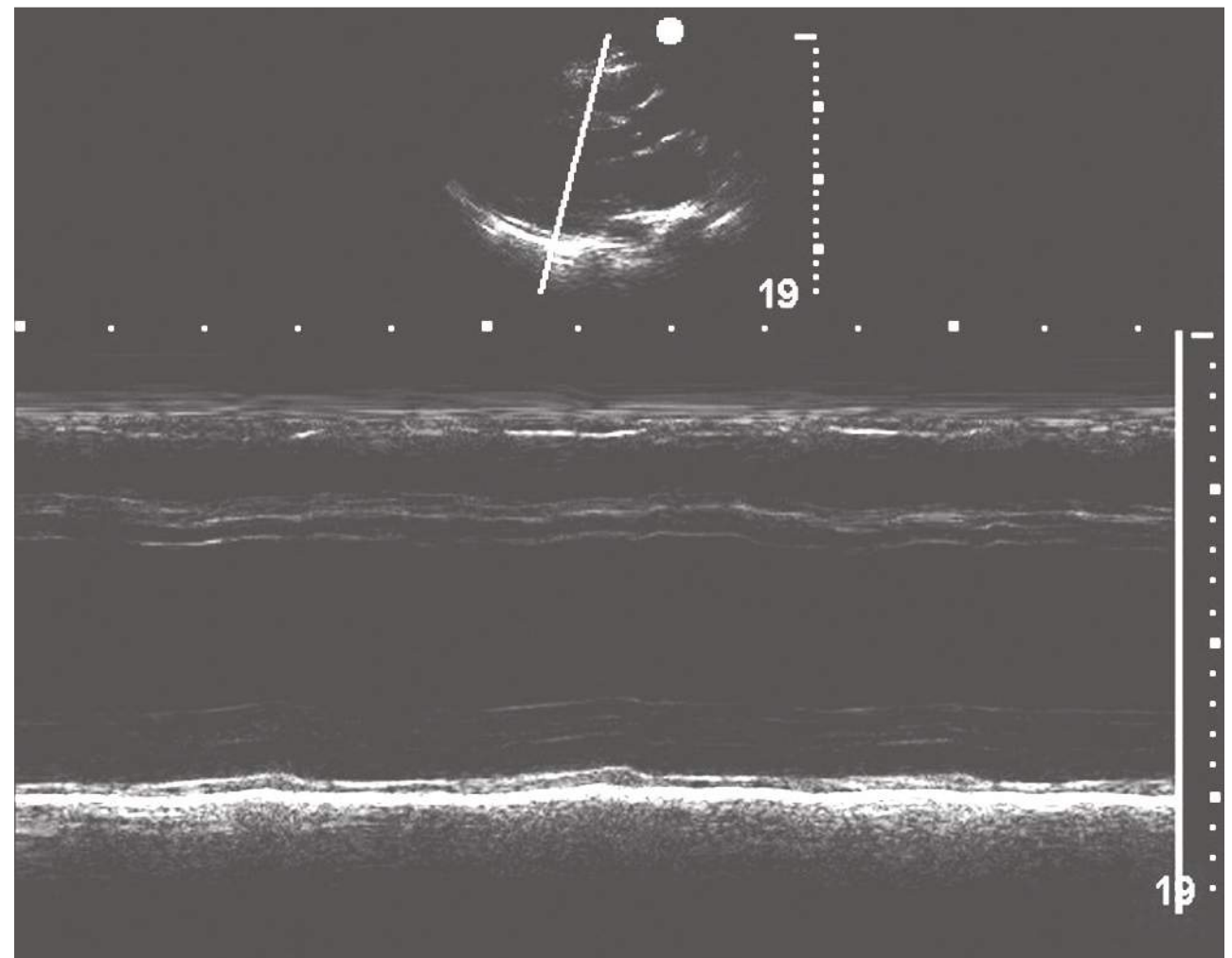


FIGURE 53-31 Parasternal long-axis M-mode view, poor ejection fraction. Parasternal long-axis M-mode view at the level of the papillary muscles with M-mode with marker bisecting the left ventricle. Note the severely reduced left ventricular (LV) systolic function as evidenced by the dilated LV, minimal change in LV diameter, and poor ventricular wall thickening during systole.

calculate a measured ejection fraction (Figure 53-36). Ejection fraction is calculated from fractional shortening from the following formula: $EF = ([\text{LV end-diastolic diameter}]^3 - [\text{LV systolic diameter}]^3) / ([\text{LV end-diastolic diameter}]^3)$. This is best performed in the parasternal long- or short-axis views. This technique is easy to learn and perform but has several drawbacks. Measurements must be completely perpendicular to the ventricle, accurate, and avoid overestimating or underestimating the measurements, as any measurement error is compounded by cubing of values. In addition, this measurement assumes symmetric ventricular contraction

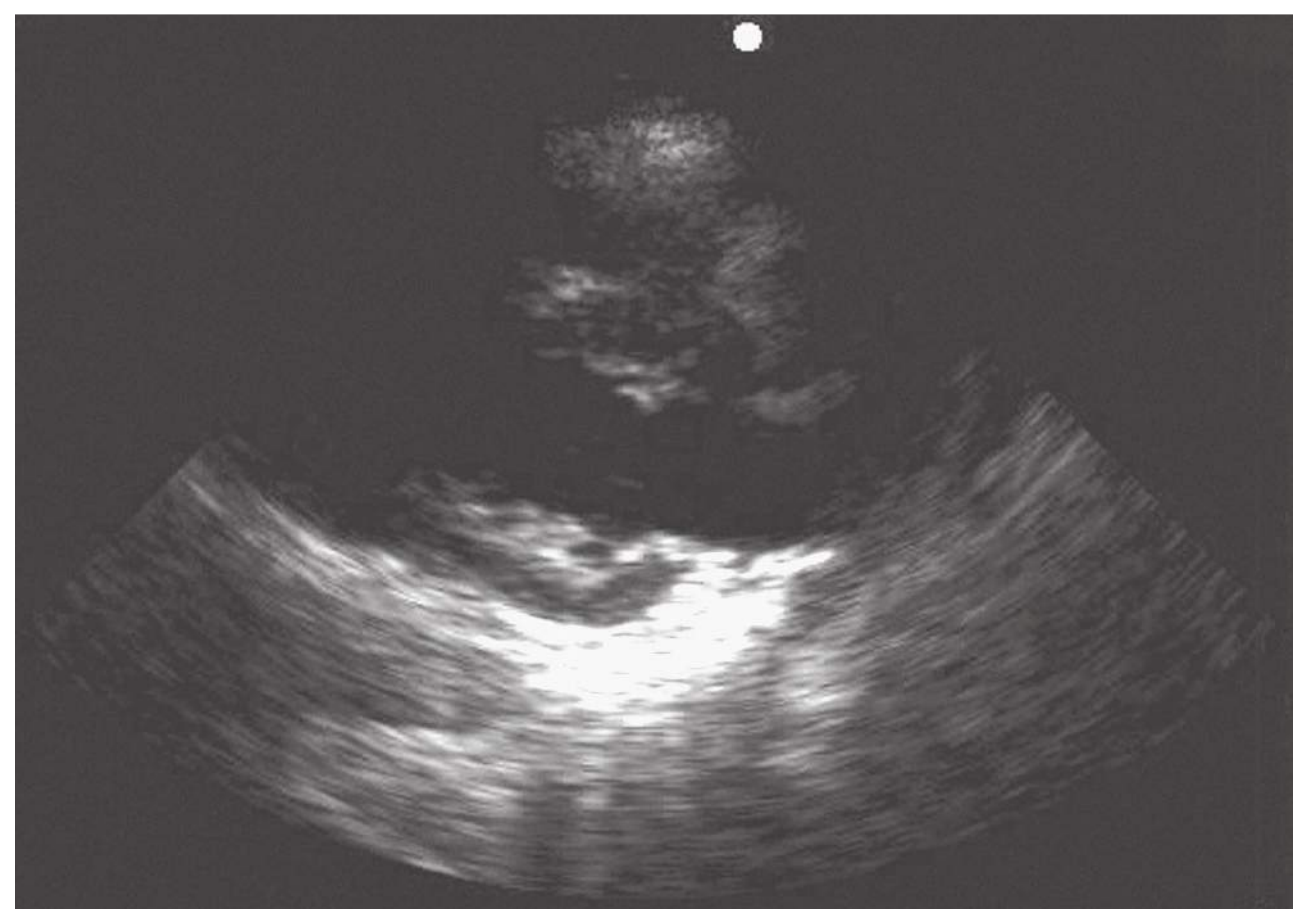


FIGURE 53-32 Parasternal long-axis view, normal ejection fraction, normal mitral valve (MV) motion. Parasternal long-axis view during mid-diastole showing maximal MV opening in a heart with normal systolic function. Note the anterior MV leaflet almost touching the septum.

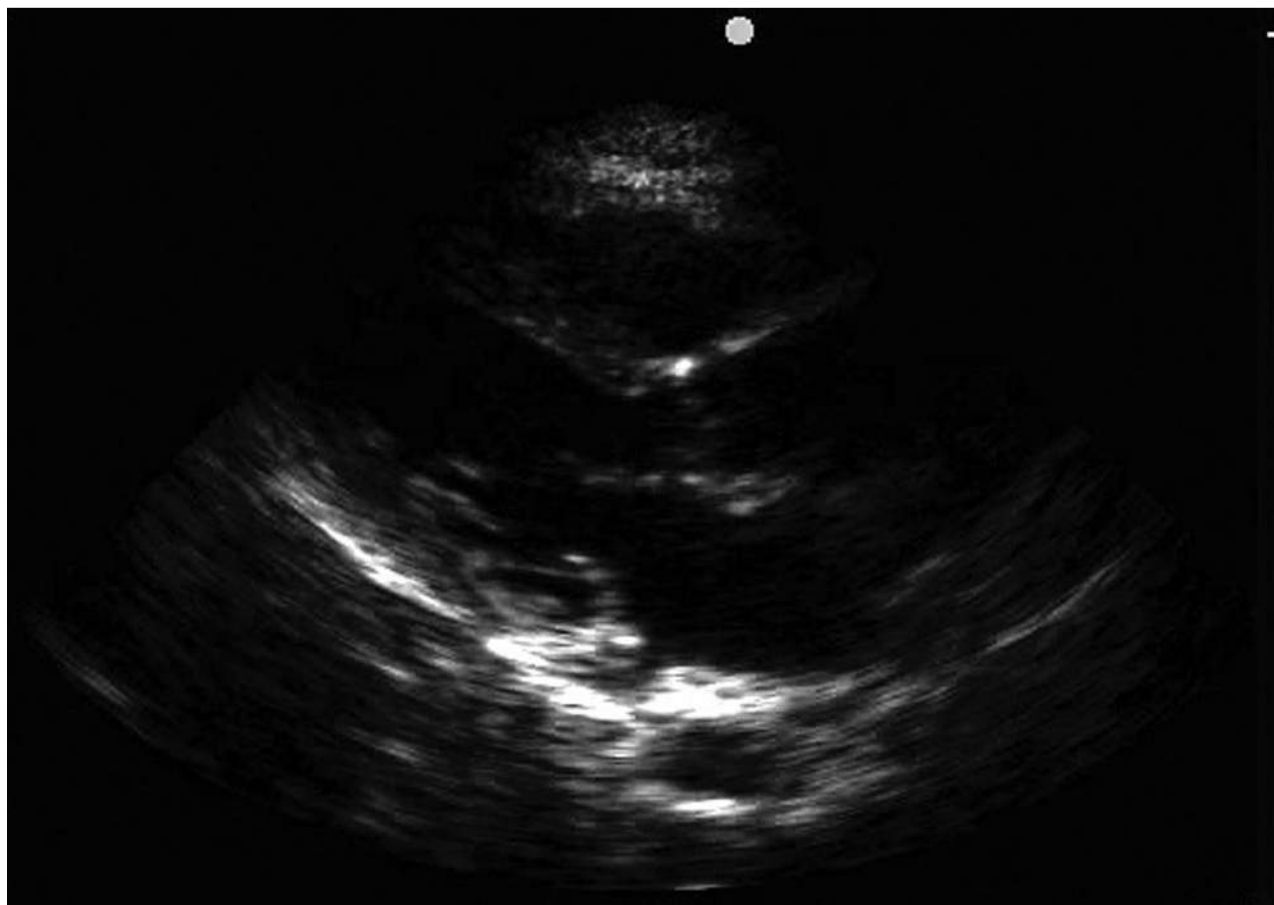


FIGURE 53-33 Parasternal long-axis view, low ejection fraction, abnormal mitral valve (MV) motion. Parasternal long-axis view during mid-diastole showing maximal MV opening in a heart with abnormal systolic function. Note that the anterior MV leaflet is > 1 cm from the septum, indicating elevated left ventricular (LV) pressure and diminished LV function.

without differences in wall motion. In the setting of asymmetrical hypokinesis, this method will overestimate LV systolic function.

Left ventricular systolic function can also be estimated using Simpson's method of discs. To perform this method, an apical four-chamber view is obtained. End diastole should be identified and the image frozen. The LV area can be traced using a caliper along the endocardial border. LV volume in diastole

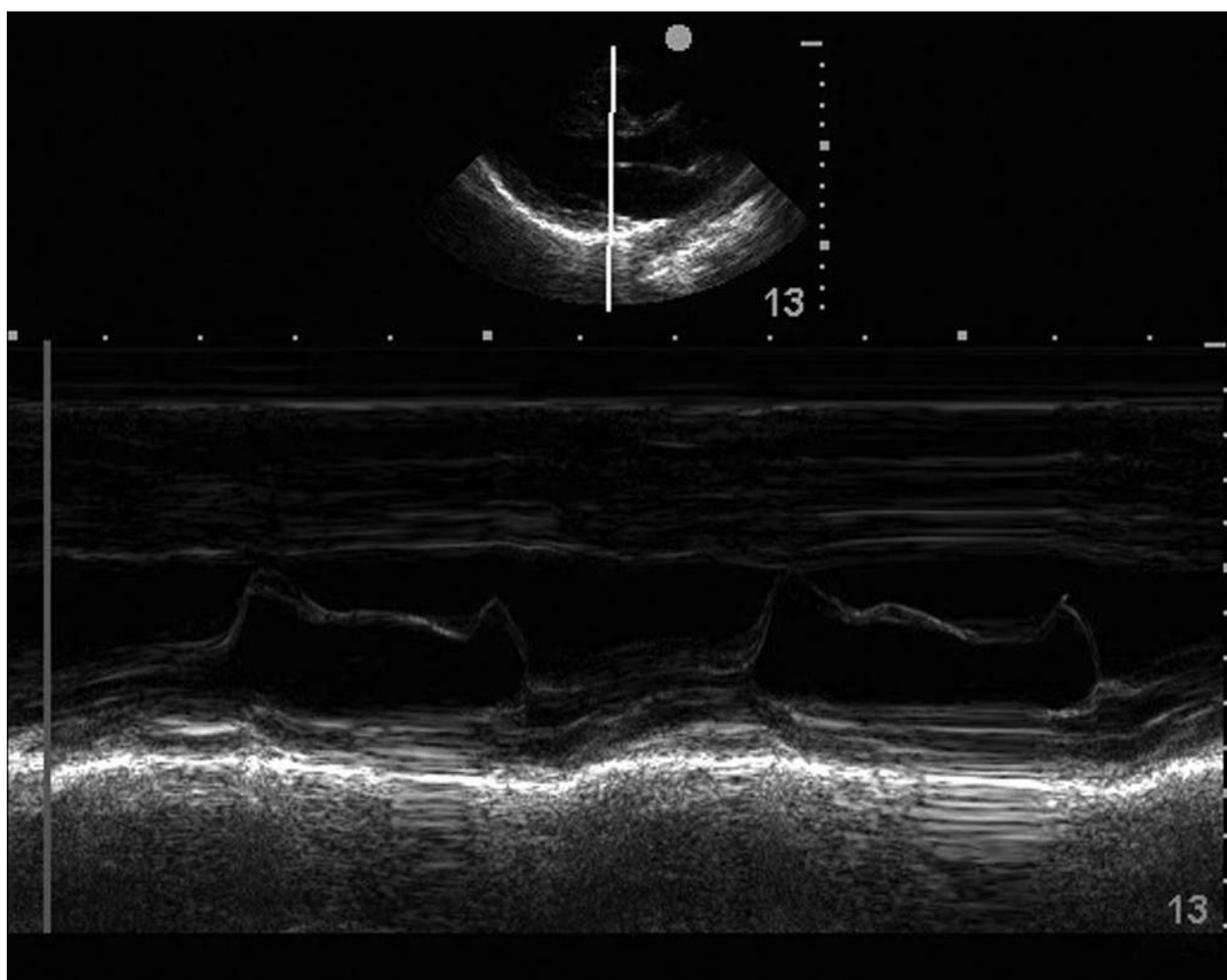


FIGURE 53-34 Parasternal long-axis M-mode view, normal ejection fraction, normal E-point septal separation (EPSS). Parasternal long-axis M-mode view with M-mode with marker across the anterior mitral valve (MV) leaflet, with the movement of the anterior MV leaflet plotted versus time. The first peak in its excursion represents the E point; it corresponds to MV inflow secondary to ventricular relaxation. The second peak, the A point, is secondary to MV inflow from atrial contraction. Note the normal EPSS within the normal range of < 0.85 cm.

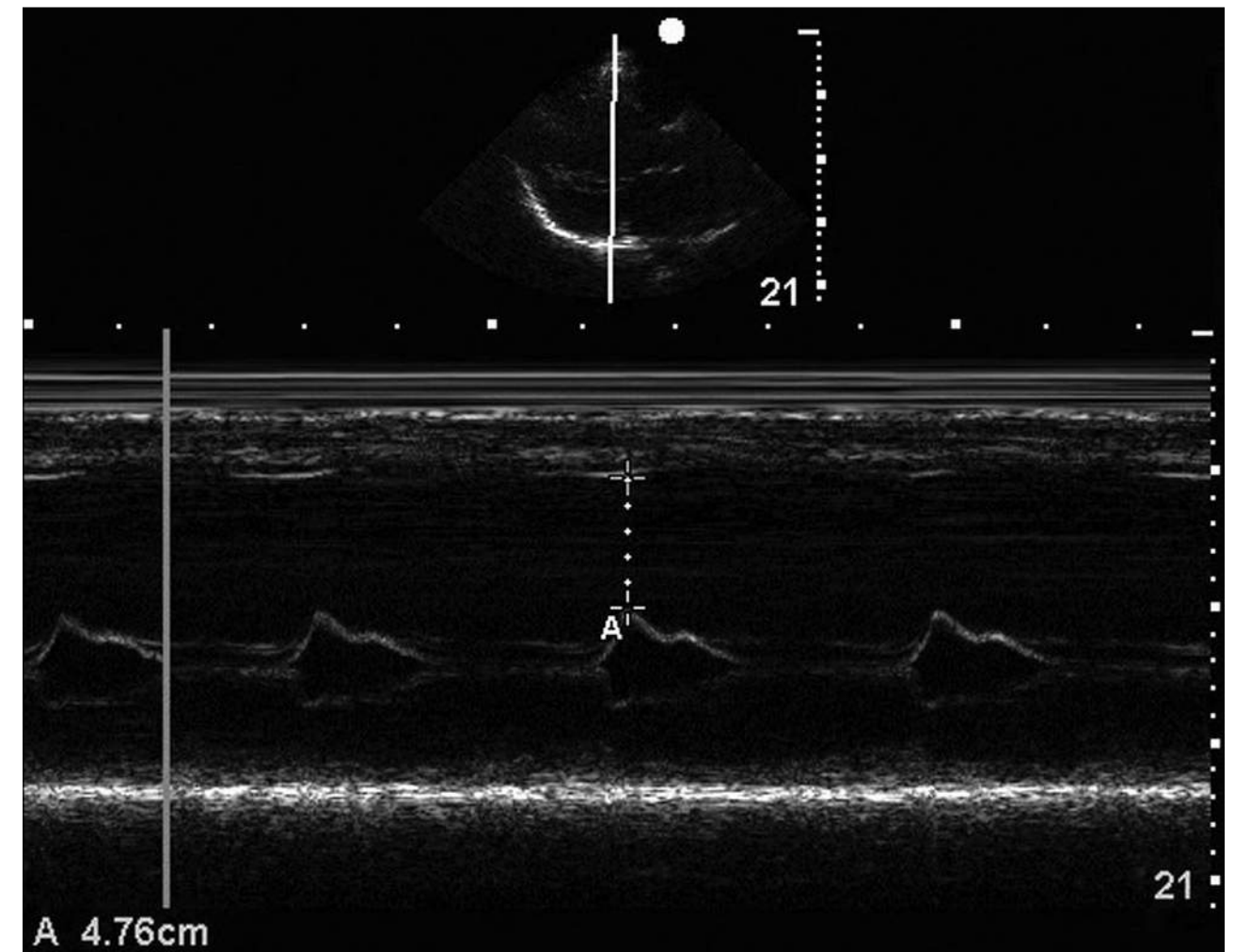


FIGURE 53-35 Parasternal long-axis M-mode view, poor ejection fraction, abnormal E-point septal separation (EPSS). Parasternal long-axis M-mode view with M-mode with marker across the anterior mitral valve (MV) leaflet, with the movement of the anterior MV leaflet plotted versus time. Note the markedly increased EPSS. This is most commonly secondary to reduced left ventricular function, but can also be seen in mitral stenosis and aortic regurgitation.

will be calculated by the ultrasound machine by the creation of several small virtual discs within the LV cavity (Figure 53-37). Once the LV end-diastolic volume is calculated, a view of the LV at end systole is obtained. Again, the endocardial border is traced to obtain the LV area, which allows calculation of the LV end-systolic volume. Once the end-diastolic and end-systolic volumes are calculated, ejection fraction will be calculated by the following formula: $EF = (\text{end-diastolic LV volume} - \text{end-systolic LV volume}) / \text{end-diastolic LV volume}$. For increased accuracy, the procedure can be repeated in the apical two-chamber view, obtained by rotating the transducer

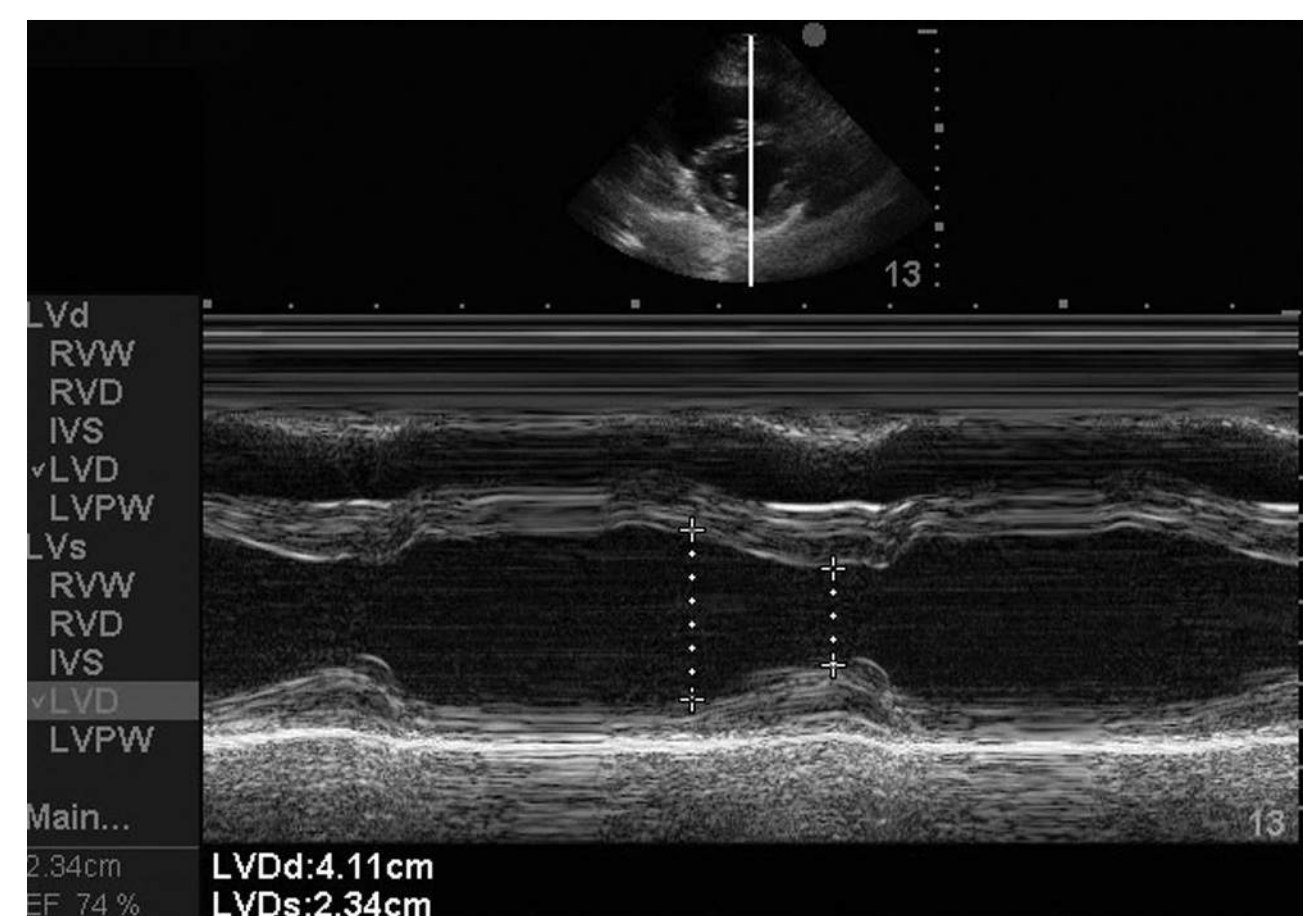


FIGURE 53-36 Parasternal short-axis M-mode view, normal ejection fraction (EF). Parasternal short-axis M-mode view at the level of the papillary muscles with M-mode with marker bisecting the left ventricle (LV). Using the LV end-diastolic (LVDd) and end-systolic diameters (LVDs), both fractional shortening and EF can be calculated.



FIGURE 53-37 Apical four-chamber view showing use of Simpson's method of discs to calculate left ventricular ejection fraction. End-diastolic volume (a) is estimated at 163 mL, and end-systolic volume (b) is estimated at 53 mL, yielding ejection fraction of 67%.

90 degrees counterclockwise from the apical four-chamber view. This method, although more accurate than simple use of fractional shortening, has disadvantages. It is more time-consuming, the endocardial border can be difficult to clearly visualize, and errors can be made in identifying which frames represent end diastole and end systole.

Doppler echocardiography can also be used to quantitatively estimate stroke volume and cardiac output using the velocity–time integral (VTI) of LVOT, along with the LVOT D and heart rate. This method compares favorably with traditional pulmonary artery catheter thermodilution methods. A parasternal long-axis view is obtained and the aortic root and aortic valve leaflets are identified. The LVOT D is measured at the beginning of systole at the location of insertion of the aortic valve leaflets. The US system uses this measurement to calculate the LVOT cross-sectional area (Figure 53-38). An apical five-chamber view is then obtained by angling the transducer slightly anteriorly. Using spectral pulsed wave Doppler with the sample gate at the exact position where the LVOT D was measured, velocity over time is measured (Figure 53-39). It is very important to align the Doppler marker as parallel as possible to blood flow through the LVOT to avoid measurement error. Using the calculator package, the exterior of the

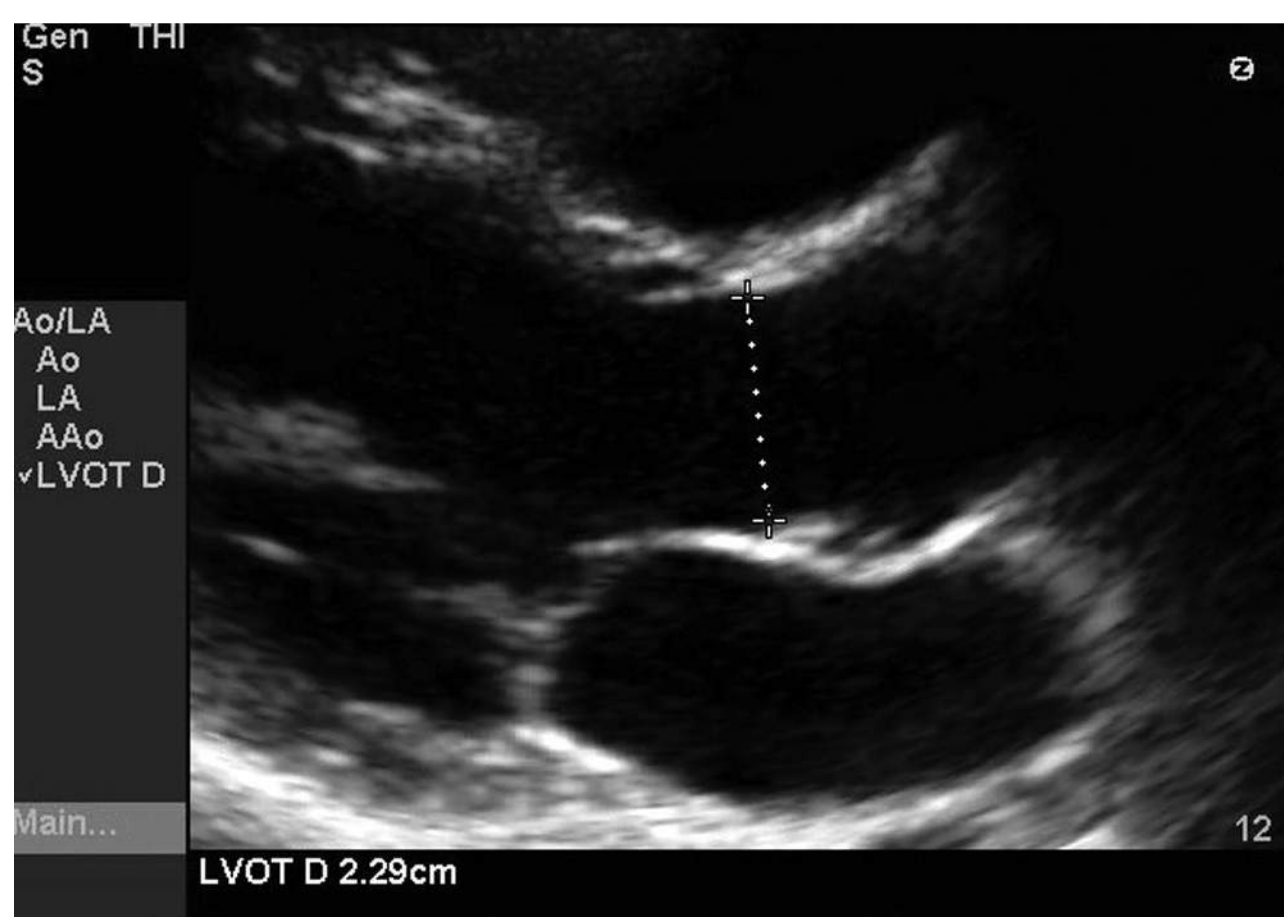


FIGURE 53-38 Parasternal long-axis view demonstrating correct measurement of left ventricular (LV) outflow tract diameter at the aortic valve leaflet point of attachment. The US system will use this measurement to calculate LV outflow tract area.

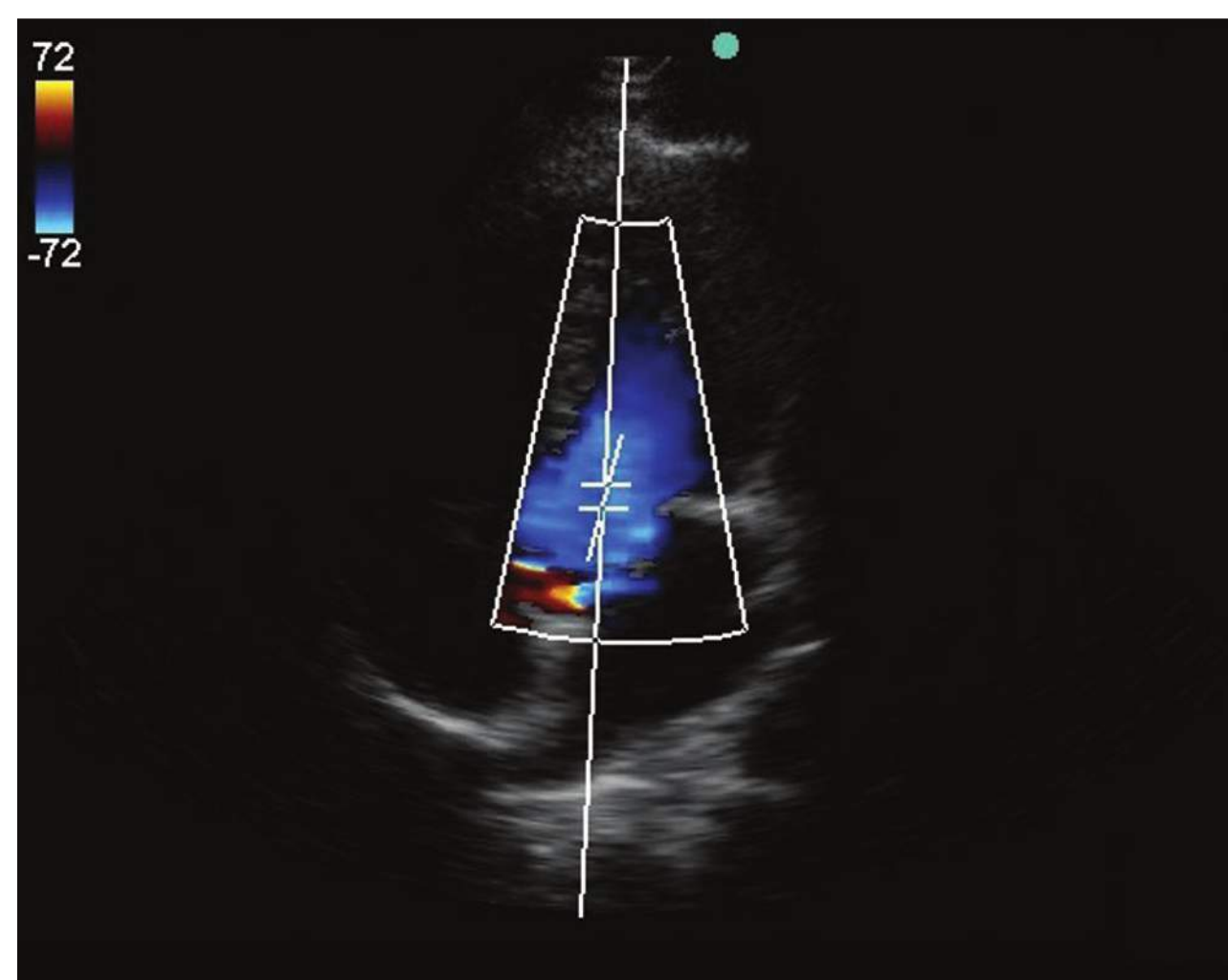


FIGURE 53-39 Apical five-chamber view showing the spectral Doppler gate within the left ventricular (LV) outflow tract. Note the blue color indicating flow away from the transducer and the vector adjustment of the Doppler gate to be within the LV outflow tract.

velocity curve is then traced to determine the VTI. The area under the velocity curve is the VTI, and most systems will calculate this value automatically (Figure 53-40). The stroke volume equation is $SV = \pi r^2 \times \text{LVOT VTI}$ (where r is the radius of the LVOT), and cardiac output can be calculated by multiplying stroke volume and heart rate.

DIFFERENTIATING HYPOVOLEMIA FROM LOW SYSTEMIC VASCULAR RESISTANCE

The LV will appear hyperdynamic and the LVEF will be elevated in cases of intracardiac hypovolemia and in cases of

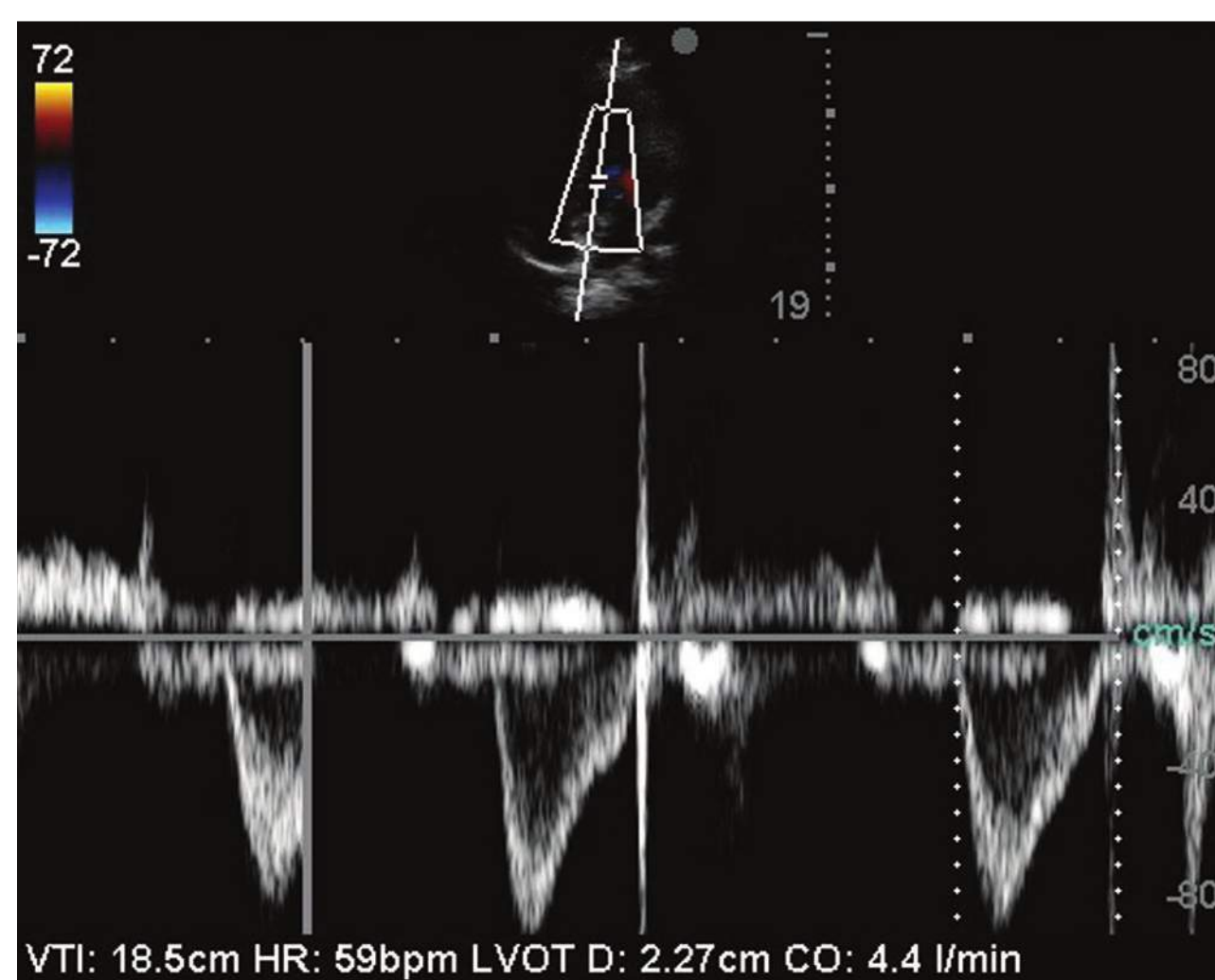


FIGURE 53-40 LV outflow tract (LVOT) pulsed wave Doppler. LVOT velocity is plotted under the baseline, blood is moving away from the transducer. The area under the curve is the velocity–time integral (VTI). Using the measured VTI and LVOT diameter, the US system can calculate stroke volume.

low systemic vascular resistance. While hypovolemia and low vascular tone can occur simultaneously, for example in sepsis prior to fluid resuscitation, methods have been developed to differentiate these two problems when one occurs in the absence of the other. At times, hypovolemia is obvious, with an LV cavity that completely collapses 100% with each systole. This is sometimes called the “kissing ventricle” sign, as the endocardial borders of opposite walls actually touch at end-systole. It is important to note that “kissing ventricle” may also be present in low vascular tone. The key to differentiate between low systemic vascular resistance and low volume on echocardiography lies within the diameter of the LV in diastole.

A simple method for evaluating for hypovolemia is the measurement of the LV internal diameter at end-diastole (LVIDd), typically performed in the parasternal long-axis view just beyond the tips of the mitral leaflets. Normal LVIDd is 4.2–5.9 cm for men and 3.9–5.3 cm for women. In the setting of hypotension and shock, an LVIDd that is significantly lower than these normal values is suggestive of hypovolemia. In a low-vascular tone state, the diameter in systole will be small, but the patient will have a normal LVIDd.

An echocardiographic method for determining fluid responsiveness is analysis of the change in stroke volume with passive straight leg raise. This is performed by first measuring the stroke volume by the LVOT VTI method while the patient is in a semi-recumbent position (legs flat on the bed and torso angled at 45 degrees). The stroke volume is then re-measured with the patient flat on his or her back with straight legs raised at 45 degrees. If this maneuver increases the stroke volume by $\geq 15\%$, then the patient is considered “fluid responsive,” and the clinician can expect that a fluid bolus of ≥ 500 mL will increase cardiac output by at least 15%.

The systemic vascular resistance (SVR) can be calculated with echocardiographic data and a few additional data points: the mean arterial pressure (MAP) and the CVP. This is because $SVR = (MAP - CVP)/\text{cardiac output}$. The LVOT VTI method of calculating stroke volume can be used, the MAP is readily available either by noninvasive blood pressure measurement or from an arterial catheter, and the CVP can either be measured with a central venous catheter or estimated by imaging of the IVC (described later). In pure hypovolemic states, the SVR will be markedly elevated as capacitance vessels constrict to restore central volume.

Echocardiography to Estimate Central Venous and RV Filling Pressures

Physicians can accurately estimate central venous and RV filling pressure using point-of-care echocardiography. Key methods for estimation of CVP include assessment of IVC diameter and IVC collapsibility index. These measures correlate with CVP and can be helpful in differentiating hypovolemia, patients in septic shock who will respond to fluid resuscitation, tamponade physiology, fluid overload states such as CHF, tamponade physiology, and elevated RV pressures in suspected pulmonary embolus.

The IVC is a thin-walled high-capacitance vessel that carries about 80% of the venous return to the right atrium. Its route is purely abdominal and is subject to intra-abdominal pressure and right atrial pressure, and thus its volume and pressure dynamics are related to the body's volume status. Several recent studies have shown that the size of the IVC likely correlates to intravascular volume status. Zengin et al.²¹ showed that IVC size was small in hypovolemic patients, and Yavasi et al.²² showed that IVC size is elevated in fluid overload states and reduces after diuretic therapy.

The physiology of this capacitance vessel allows us to extrapolate the pressure and volume changes that occur during the cardiac and respiratory cycles. The IVC contracts and expands with each respiration. Negative pressure created by the inspiration of a spontaneously breathing patient increases venous return to the heart, briefly collapsing the IVC. Exhalation decreases venous return and the IVC returns to its baseline diameter. In patients who are mechanically ventilated, the relationship is reverse. Positive pressure occurs with inspiration, decreases venous return, and keeps the IVC at a baseline diameter. During expiration on the ventilator, negative pressure is created, thus increasing venous return and briefly collapsing the IVC.

There is encouraging data to suggest that IVC size correlates with CVP measurement in patients with central lines (discussed in detail later). Normal variation with inspiration is about a 50% reduction in IVC diameter. CVP is estimated using both the IVC diameter and percent change during respiration. This estimation correlates with CVP best at the extremes, which is the most clinically relevant scenario. Using this technique, emergency physicians can rapidly and accurately diagnose the low and high CVP noninvasively.

There are also continued data to suggest that the state of intravascular volume correlates with the percentage collapse of the IVC. For example, in states of low intravascular volume, the percentage collapse of the vessel will be proportionally higher than in intravascular volume overload states. This is quantified by the calculation of the IVC collapsibility index or the caval index: $\text{IVC maximum diameter} - \text{IVC minimum diameter} / \text{IVC maximum diameter} \times 100 = \text{caval index (\%)}$. The caval index is written as a percentage, where a number close to 100% is indicative of almost complete collapse (and therefore volume depletion), whereas a number close to 0% suggest minimal collapse (i.e., likely volume overload). Certain obstructive physiologies like tamponade will demonstrate a large, noncollapsible IVC.

The standard location to measure the IVC diameter is just distal to the IVC and hepatic vein junction because the IVC is fixed at the diaphragm, which limits evaluation for respiratory variation. The diameter of the IVC for calculation of the caval index should be measured in the longitudinal plane, approximately 2 cm from where it enters the right atrium. For calculation of the caval index, one should measure the caval diameters in M-mode to visualize the respiratory variation (Figures 53-41 and 53-42). The M-mode beam should be overlying the IVC 2 cm from the right atrium (which is approximately at the level where the hepatic vein joins the

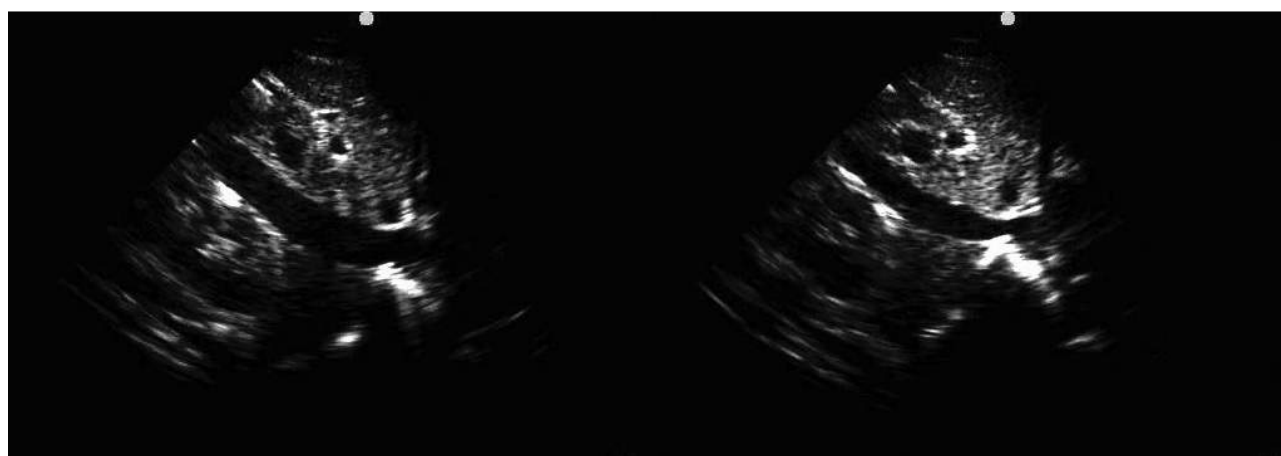


FIGURE 53-41 Subxiphoid inferior vena cava (IVC) view, normal IVC diameter and respiratory change. Subxiphoid IVC view showing the IVC in (a) expiration and (b) inspiration, with normal IVC diameter and inspiratory collapse of approximately 50%.

IVC). The inspiratory and expiratory diameter can then be measured on the M-mode image, at the smallest and largest locations. The normal diameter of the IVC in adults is between 1.5 and 2.5 cm. Patients with low volume will tend to have IVC diameters < 1.5 cm, whereas patients with volume overload will tend to have IVC diameters > 2.5 cm. With inspiration, thoracic pressure becomes negative, leading to increased venous return and a smaller IVC diameter. This can be accentuated and more accurately measured using M-mode (Figures 53-41 and 53-42).

Several studies suggest that IVC diameter can predict the CVP. A recent prospective observational study enrolled 102 patients undergoing right heart catheterization and echocardiography.²³ Initial receiver operating characteristics were analyzed to determine optimal cutoffs, which were then prospectively studied. An IVC diameter of 2 cm correctly predicted RAP (right atrial pressure) above or below 10 with a sensitivity and specificity of 73% and 85%, respectively, and a collapsibility of 40% performed similarly with sensitivities and specificities of 73% and 84%, respectively.

Another recent study showed that $> 50\%$ collapse of the IVC with inspiration was sensitive and specific for a CVP

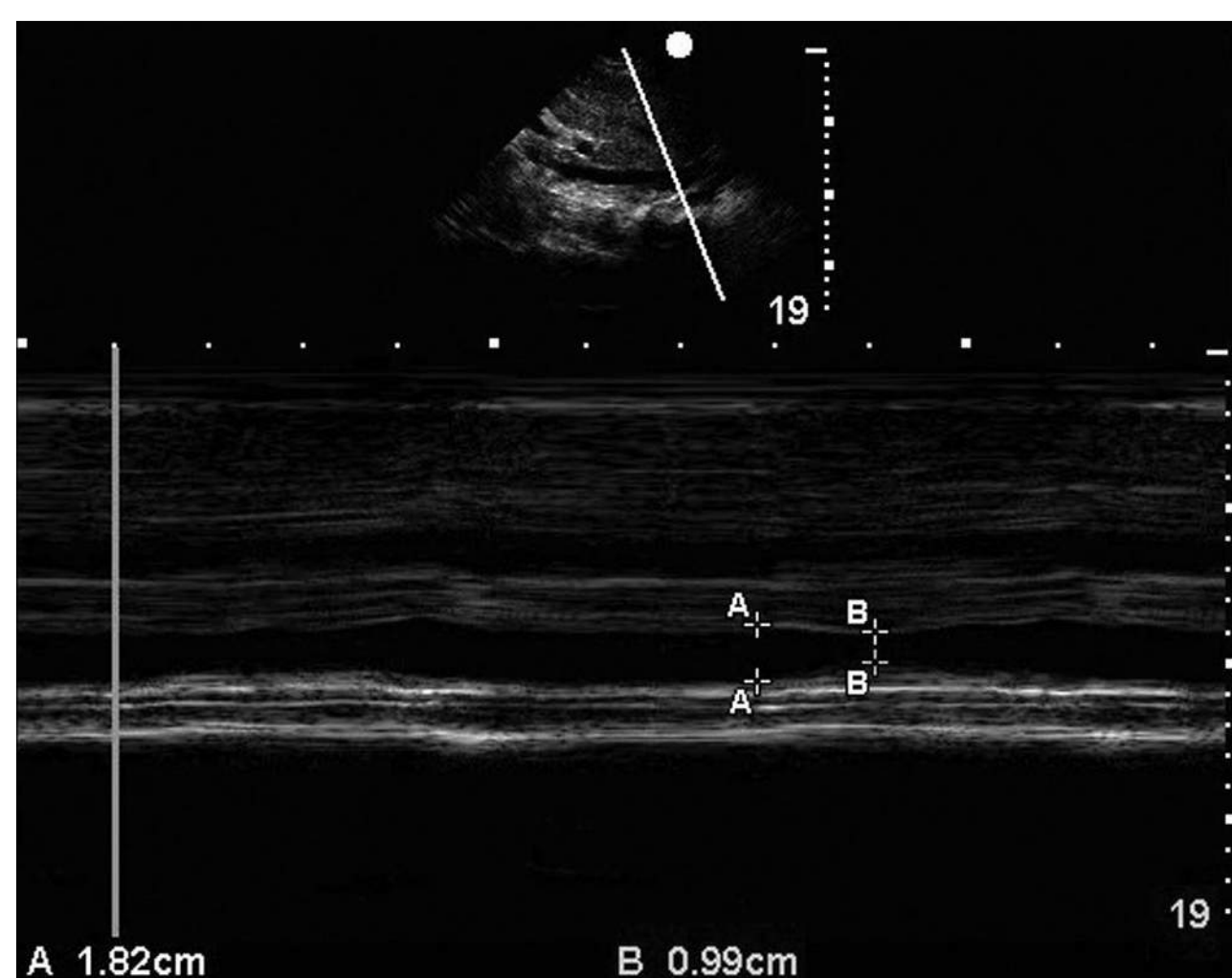


FIGURE 53-42 Subxiphoid inferior vena cava (IVC) M-mode view showing the IVC in (a) expiration and (b) inspiration, with normal IVC diameter and normal inspiratory collapse of approximately 50%.

measurement of < 8 mm Hg.²⁴ This prospective observational study enrolled 73 patients who were undergoing central venous catheterization. Ultrasound measurements of the IVC during inspiration and expiration were performed, and the caval index was calculated. They found $> 50\%$ collapse was associated with CVP of < 8 mm Hg with a sensitivity of 91%, a specificity of 94%, positive predictive value of 87%, and negative predictive value of 96%.

Several studies have shown that a flat IVC and elevated collapsibility index is an accurate and sensitive marker of hypovolemia. Of note, these studies are small in size and have several limitations. One study showed that IVC diameter correlated with hypovolemia in trauma patients.²⁵ This prospective observational study enrolled 35 victims of trauma, 10 patients found to be in shock, defined as an SBP < 90 mm Hg on arrival or within 12 hours of arrival, and a control group of 25 hemodynamically stable patients. The mean diameter of the IVC was much smaller at 7.7 mm in the shock group, compared with 13.4 mm in the control group. Subjects were also divided into two groups based on IVC diameter. Those with an IVC diameter of ≤ 9 mm had significantly larger blood transfusion volume, 11.3 U versus 0.3 U. Another study by the same authors showed that in patients being resuscitated in the presence of hemorrhagic shock, IVC diameter could predict recurrence of shock.²⁶ This prospective observational study enrolled 30 patients with hemorrhagic shock who, after enrollment, were fluid resuscitated until SBP was > 90 mm Hg. All patients then had IVC diameter recorded using bedside sonography. Patients were subsequently divided into two groups: those who remained stable after initial resuscitation (13 patients) and those who experienced recurrence of hypotension (17 patients). These two groups had no significant differences in vital signs after fluid resuscitation. However, those who experienced recurrence of shock had significantly smaller IVC diameters, 6.5 ± 0.5 mm versus 10.7 ± 0.7 mm ($P < .05$). A flat, collapsible IVC should prompt aggressive fluid resuscitation (Figures 53-43 and 53-44) because this would correlate with a low CVP and likely hypovolemic state.

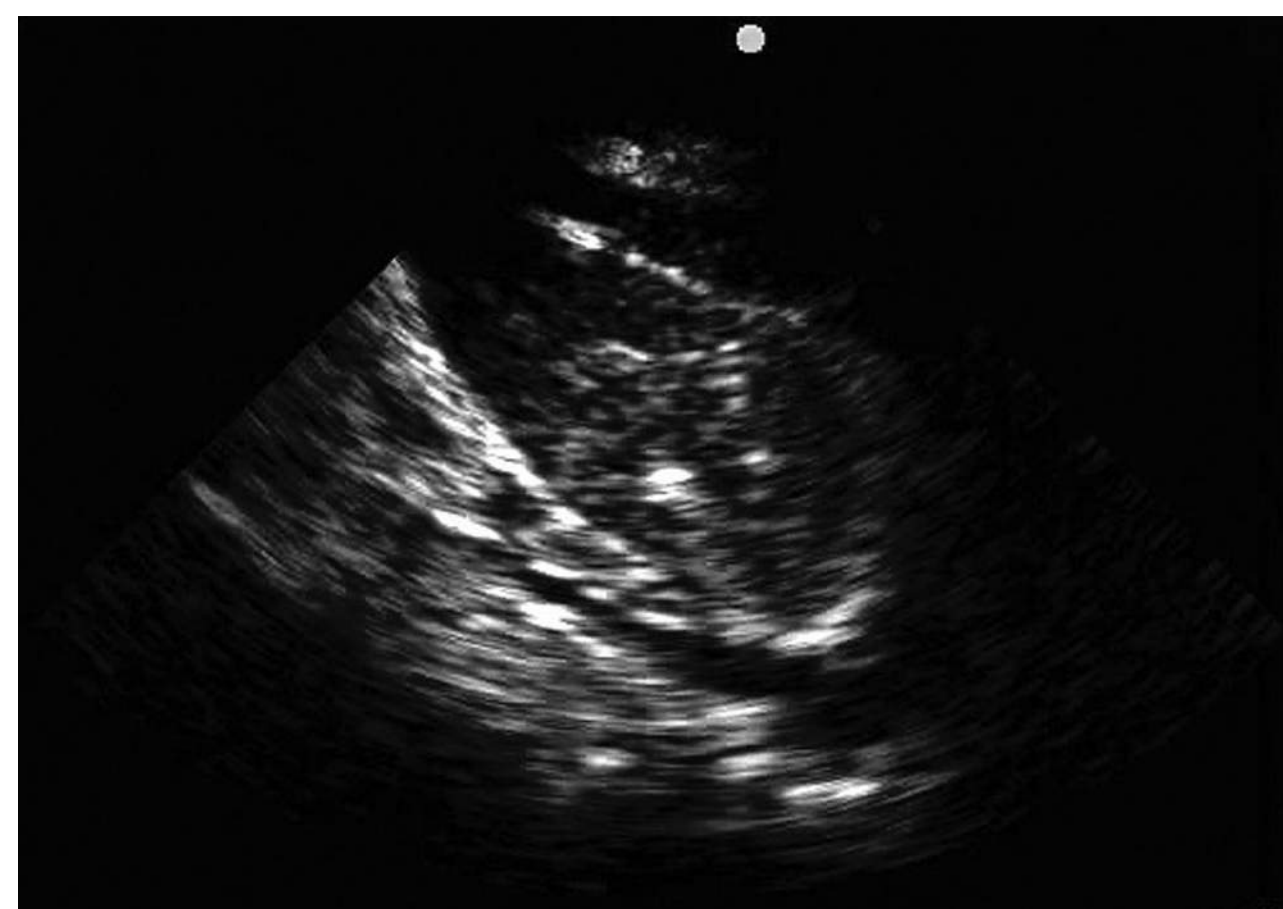


FIGURE 53-43 Subxiphoid inferior vena cava (IVC) view showing a flat IVC with a diameter < 1.5 cm, indicating low central venous pressure.

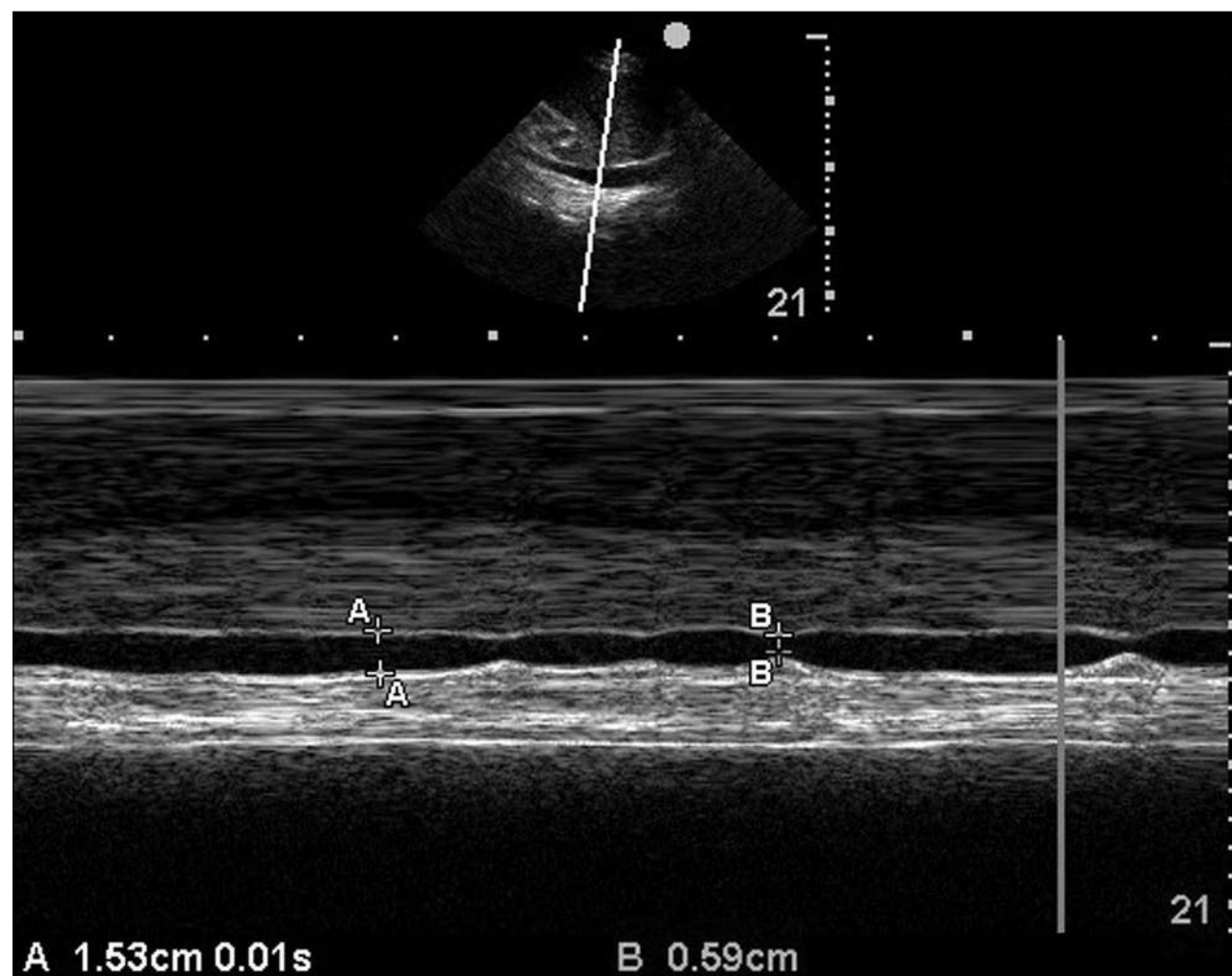


FIGURE 53-44 Subxiphoid inferior vena cava (IVC) M-mode view showing flat IVC with a diameter < 1.5 cm, with respiratory collapse of $> 50\%$, indicating decreased central venous pressure.

A recent meta-analysis evaluating the role of IVC diameter as it relates to volume status looked at 5 studies with 86 cases and 189 controls.²⁷ Maximal IVC diameter was significantly lower in hypovolemic status compared with euvolemic status; mean difference (95% confidence interval) was 6.3 mm (6.0–6.5 mm). Of note, none of the studies blinded interpreters for volume status of participants. The authors suggested that a moderate level of evidence suggests that the IVC diameter is consistently low in hypovolemic status when compared with euvolemic.

In addition, a recent prospective study²⁸ analyzed 320 IVC-CI/CVP measurement pairs from 79 patients demonstrated that IVC-CI and CVP correlate inversely, with each 1 mm Hg of CVP corresponding to 3.3% median Δ IVC-CI. Low IVC-CI ($< 25\%$) is consistent with euvolemia/hypervolemia, whereas IVC-CI of $> 75\%$ suggests intravascular volume depletion. The presence of PEEP results in 2 mm Hg to 3.5 mm Hg of CVP increase across the IVC-CI spectrum and lower collapsibility at low CVPs. Although IVC-CI decreased with increasing degrees of PEEP, this failed to reach statistical significance. Although this study represents a step forward in the area of intravascular volume estimation using IVC-CI, there were several methodological limitations that make the data not ready for standard generalization.

Likewise, additional studies have shown that a dilated IVC and low collapsibility index is an accurate marker of volume overload. One prospective observational study enrolled 75 patients hospitalized for acute decompensated CHF.²⁹ The authors found that predischARGE IVC diameter, collapsibility index, and BNP were predictive of the need for readmission. Another study showed the IVC caval index to be useful in the ED to diagnose congestive heart failure.³⁰ This prospective observational study enrolled 46 patients presenting to the ED with dyspnea. IVC caval index was determined prior to initiation of therapy, and patients with a final diagnosis



FIGURE 53-45 Subxiphoid inferior vena cava (IVC) view showing a dilated IVC with a diameter > 2.5 cm, indicating elevated central venous pressure.

of CHF were compared with those who had an alternative final diagnosis. Respiratory variation in patients with CHF was smaller than in those without CHF—9.6% versus 46%. Receiver operating characteristic curve analysis with a cut-off of 15% yielded a sensitivity of 92% with 84% specificity (Figures 53-45 and 53-46).

As previously mentioned, IVC collapsibility can also be measured in mechanically ventilated patients as well. There are a few factors to consider, such as the inverse collapsibility of the IVC during expiration inside of inspiration. In mechanically ventilated patients, a $\geq 12\%$ variation identified patients likely to respond to vascular filling, in terms of increased cardiac output, from those who would not respond, with a positive predictive value of 93% and a negative predictive value of 92%.^{31,32} In both prospective observational trials, the authors enrolled a total of 52 mechanically ventilated

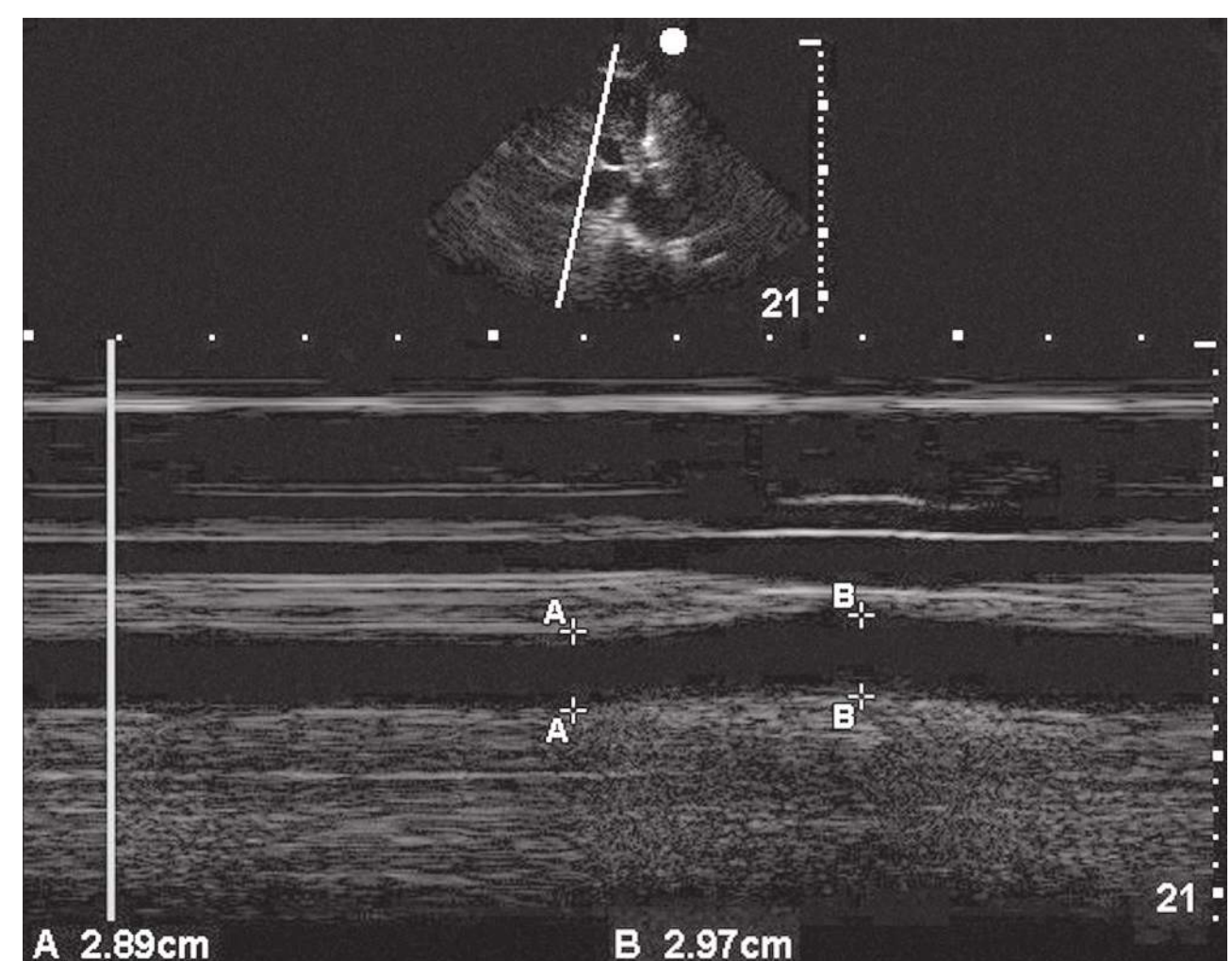


FIGURE 53-46 Subxiphoid inferior vena cava (IVC) M-mode view showing dilated IVC with a diameter > 2.5 cm, with no respiratory variation, indicating elevated central venous pressure.

patients in septic shock and also calculated the IVC distensibility as the difference between expiratory and inspiratory diameters divided by their mean IVC diameter at end expiration ($[D_{\text{max}} - D_{\text{min}}]/D_{\text{min}}$). Cardiac index was calculated using Doppler flow before and after patients received a fluid challenge. IVC distensibility $> 18\%$ identified fluid responders, those with an increase in cardiac index of at least 15% , with a sensitivity and specificity of 90% . It must be remembered that the measurements should be taken during mandatory ventilator breaths, and the tidal volume should be at least 8 mL/kg with the patient in sinus rhythm.

Thus, physicians can accurately measure IVC diameter and caval index in order to correlate with patient's fluid status and consider if the patient is fluid responsive. A recent study demonstrated a κ of 0.64 (95% cardiac input $\text{CI} = 0.53$ to 0.73) for EP ability to predict a patient's volume status based on visual estimation of IVC filling (size, shape, and collapse).³³

Common pitfalls in evaluation of the IVC include incorrect identification of the aorta, which is adjacent to the IVC. The aorta is pulsatile and will have a thicker, more hyperechoic wall, visualized as the probe is tilted toward the left side of the body. Another common pitfall is not considering the clinical scenario. For example, the IVC diameter and the caval index are isolated markers of pressures on the right atrium. A plethoric IVC may occur in clinical settings other than intravascular volume depletion such as tamponade, mitral regurgitation or aortic stenosis. Although larger studies are needed to confirm these results, this implies that IVC diameter may be a useful adjunct in predicting the clinical volume status in patients.

Evaluation of Acute Right Heart Strain

Physicians can identify acute right heart strain using point-of-care echocardiography for basic qualitative assessment. This can be very clinically helpful in the setting of massive or submassive pulmonary embolism (PE) to direct the proper course of treatment. Several signs consistent with RV strain are listed here. Although there are additional and advanced techniques to quantify the degree of RV strain, for example, two-dimensional speckle-tracking strain to quantify the RV myocardial deformation, this analysis is too time-consuming for the emergency room physician in the assessment of acute right heart strain. Specifically, in this chapter, we will further discuss (1) dilated RV, (2) septal shift of the intraventricular septum during diastole, (3) RV hypokinesis, and (4) intracardiac thrombus.

ECHOCARDIOGRAPHIC SIGNS OF RV STRAIN

- RV dilatation $> 1:1$ (normal ratio right: left ventricle is $< 0.6:1$)
- RV systolic dysfunction
- McConnell's sign: mid-RV wall hypokinesis with apical sparing
- Moderate to severe tricuspid regurgitation
- Paradoxical septal wall motion toward the LV
- Pulmonary artery dilatation

- Atrial dilatation
- Right heart thrombus or thrombus in transition
- Lack of respiratory variation of the IVC

There is limited information on the utility of certain echocardiographic measurements, such as RV strain analysis, in predicting mortality in patients with acute PE. A recent study³⁴ retrospectively evaluated 211 patients with acute PE admitted to a medical ICU and prospectively measured echocardiographic variables with a focus on ICU, hospital, and long-term mortality. The authors concluded that the four parameters that measure different aspects of the RV (ratio of RV to LV end-diastolic diameter, RV systolic pressure, tricuspid annular plane systolic excursion, and IVC collapsibility) were independently associated with mortality in patients presenting with acute PE who were admitted to the ICU.

Another recent prospective observational study by Dresden³⁵ demonstrated diagnostic performance of RV dilatation identified by emergency physicians on bedside echocardiography in 146 patients with a suspected or confirmed PE. In addition, the study explored the predictive value of a subgroup of findings associated with advanced RV dysfunction (RV hypokinesis, paradoxical septal motion, McConnell's sign). The authors concluded that RV dilatation and RV dysfunction identified on emergency physician-performed echocardiography were found to be highly specific for PE but had poor sensitivity. Right ventricular dilatation on echocardiography had a sensitivity of 50% , a specificity of 98% , and 88% both positive and negative predictive value. Positive and negative likelihood ratios were determined to be 29 and 0.51 , respectively. Certainly because of the low sensitivity, there are conditions where RV dilatation, dysfunction, and strain will be present without the diagnosis of PE. Always consider the clinical context and the fact that this study was performed on high pretest probability patients with suspected PE diagnosis. Other conditions like pulmonary hypertension, RV infarct, RV failure, or chronic obstructive pulmonary disease (COPD) may present with chronic RV strain pattern on echocardiography.

Multiple studies have shown similar findings that emergency echocardiogram could support the diagnosis of PE.³⁶ In one study, the authors conducted a prospective observational trial enrolling 124 patients with a suspected diagnosis of PE who then underwent emergent echocardiography. A study was considered positive if it displayed any two of the following signs: RV dilatation, abnormal septal motion, RV hypokinesis, elevated pulmonary artery or RV pressures, moderate to severe tricuspid regurgitation, or visualization of a clot within the RV or pulmonary artery. CT, MRI, and VQ scan identified 27 cases of PE. Echocardiography performed with a sensitivity and specificity of 41% and 91% , respectively. This study shows that a positive study in a high-risk patient should prompt treatment, but a negative study should not be used to rule out PE.

RV DILATATION

A recent study³⁷ has shown that the ratio of RV to LV diameter is strongly related to adverse outcomes in patients with

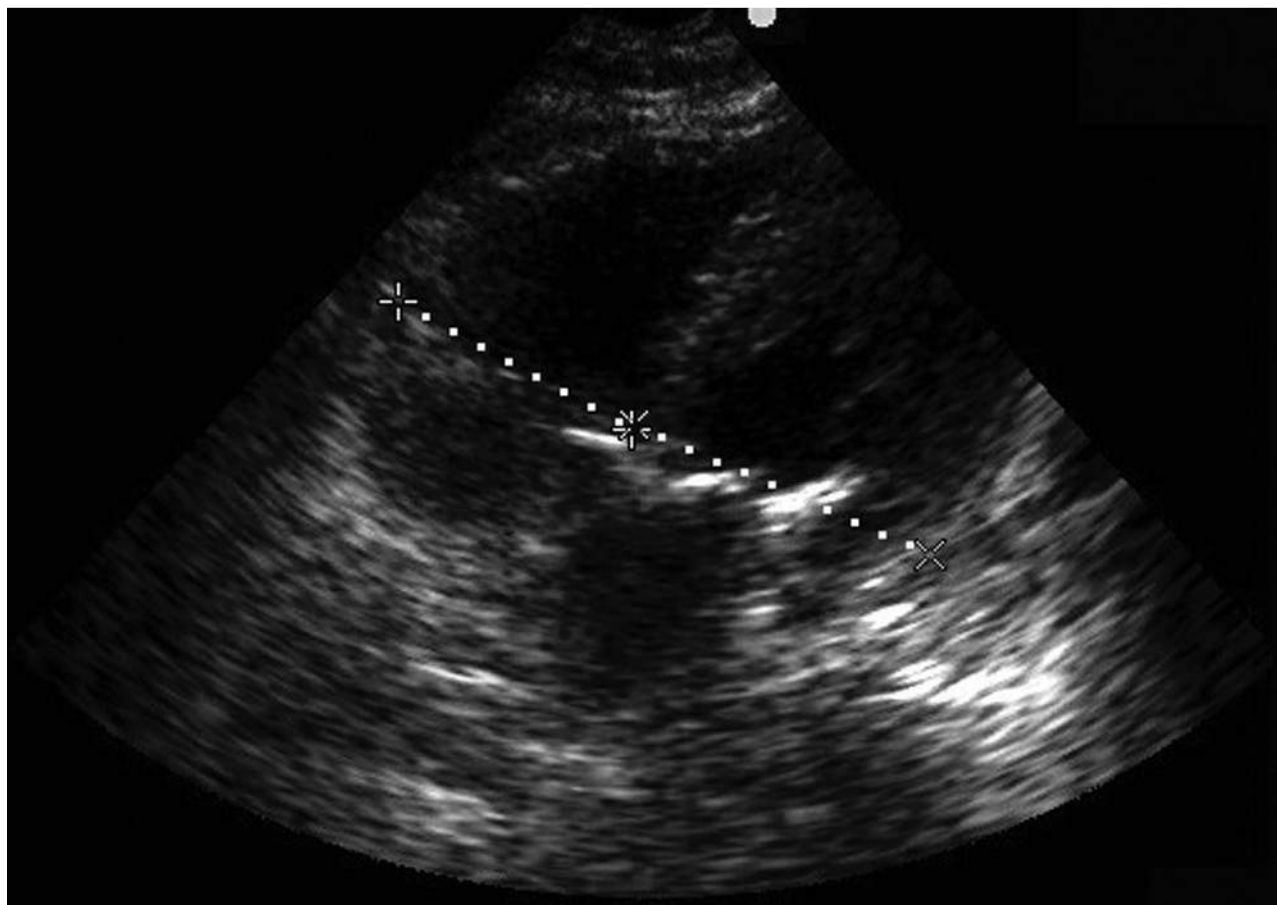


FIGURE 53-47 Apical four-chamber view showing right ventricular dilation. Note the right ventricle and left ventricle are almost equal in size at end diastole.

acute PE. The authors performed a retrospective chart review of 161 patients who were diagnosed with PE and had point-of-care echocardiographic examination. Adverse outcomes were seen in 16% or 25 patients. Adverse outcomes were defined as shock, respiratory failure requiring intubation, death, recurrent venous thromboembolism, transition to higher level of care, or major bleeding during hospital admission. Statistical analysis included univariate and multivariate analysis and showed that RV strain had a positive likelihood ratio of 4.0 and a negative likelihood ratio of 0.45. On multivariate analysis, RV strain and cardiopulmonary disease were the only predictors of adverse outcomes that achieved statistical significance, with odds ratios of 9.2 and 3.4, respectively.

The normal RV to LV ratio is $< 0.6:1$. This is best seen and measured in the apical four-chamber view, and the standard location for measurements is at the tricuspid and mitral valve leaflets (Figure 53-47). Additional views may also show RV enlargement. The subxiphoid four-chamber view may also be

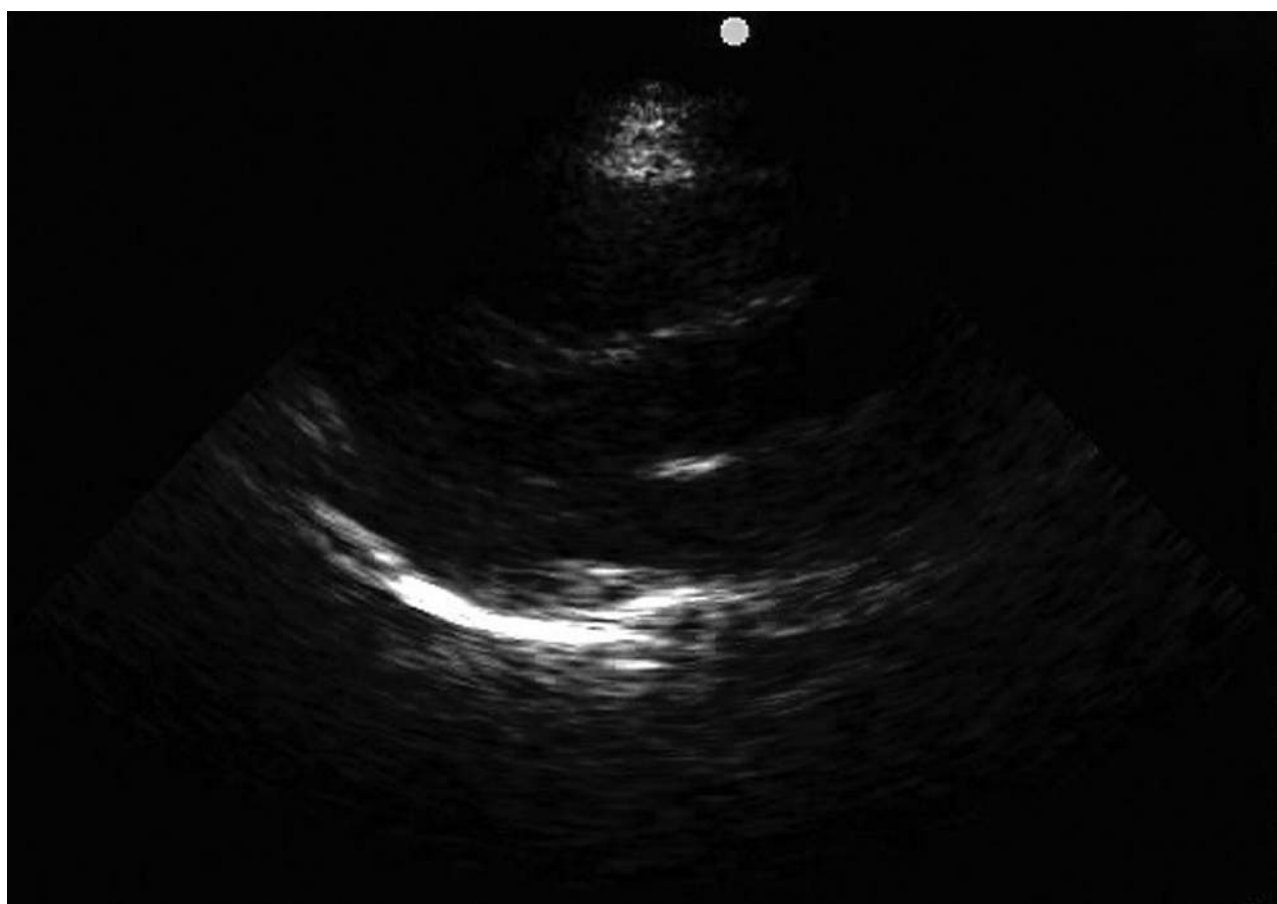


FIGURE 53-48 Parasternal long-axis view showing right ventricular dilation. Note that the right ventricle measures > 3 cm in this view. Septal flattening and bowing of the septum to the left is also seen.

used, although the transducer angle may over- or underestimate RV diameter. In the parasternal long-axis view, the RV diameter should be < 2.5 – 3 cm (Figure 53-48). A good rule of thumb for simple qualitative visual inspection is that the image should be “1/3 RV, 2/3 LV.” As pressure builds, the RV may become larger than the LV.

PARADOXICAL SEPTAL MOTION

Because the volume of the pericardium is limited, an increase in RV size with a negative left-to-right trans-septal gradient translates to a reduction in LV size (ventricular interdependence). When RV filling pressure exceeds LV filling pressure, the septum will paradoxically bow into the LV cavity during diastole. This finding is known as *septal shift* and can be best visualized in the subxiphoid four-chamber or apical four-chamber views. Assess the septum for shift during diastole by watching for paradoxical motion while the tricuspid and mitral valves are open (Figure 53-49). In the parasternal short-axis view, septal shift causes a flattening and bowing of the intra-ventricular septum. This causes a finding known as the “D sign,” as the LV cavity takes on a D-shaped appearance instead of the O-shaped appearance normally seen (Figure 53-50).

Chronic cor pulmonale can be differentiated from acute cor pulmonale by assessment of RV wall thickness and RV contractility. Over time, the RV can adapt to elevated pressures by hypertrophy of the ventricular walls. Normal RV wall thickness is < 0.5 cm, and measurements greater than this suggest RV hypertrophy. In addition, the chronically overloaded RV regains the ability to contract forcefully, and RV hypokinesis is not seen in chronic cor pulmonale.

RV HYPOKINESIS

Another finding of acute RV strain is RV hypokinesis, especially of the midventricular walls. The RV typically pumps against lower pressure, and acute pressure overload causes

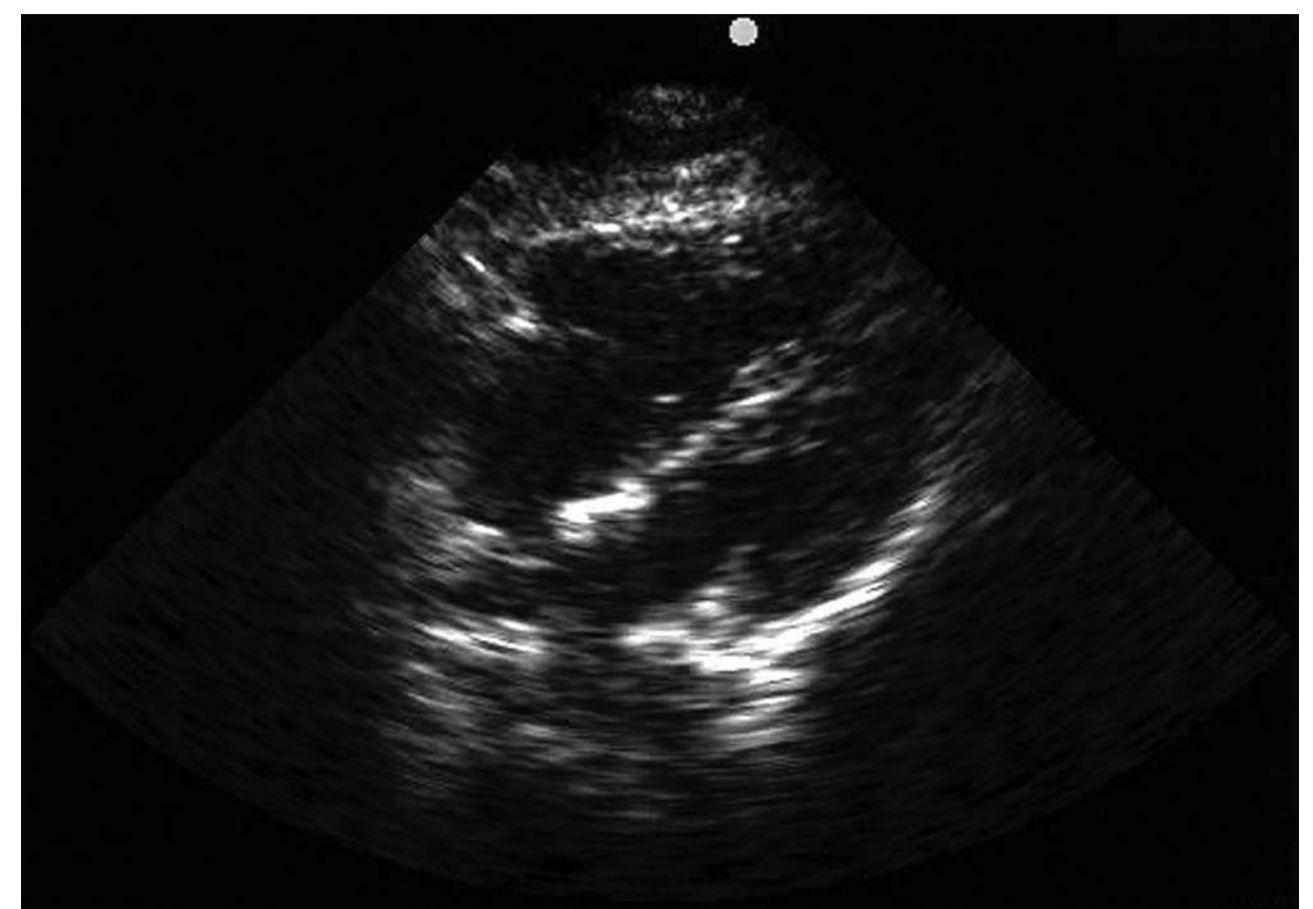


FIGURE 53-49 Subxiphoid four-chamber view showing right ventricular (RV) dilation and septal shift. Note that the RV:LV ratio is elevated above $0.6:1$. The tricuspid valve and the mitral valve are open, indicating the heart is in diastole. There is flattening of the septum toward the left ventricle in diastole, indicating elevated RV pressure.

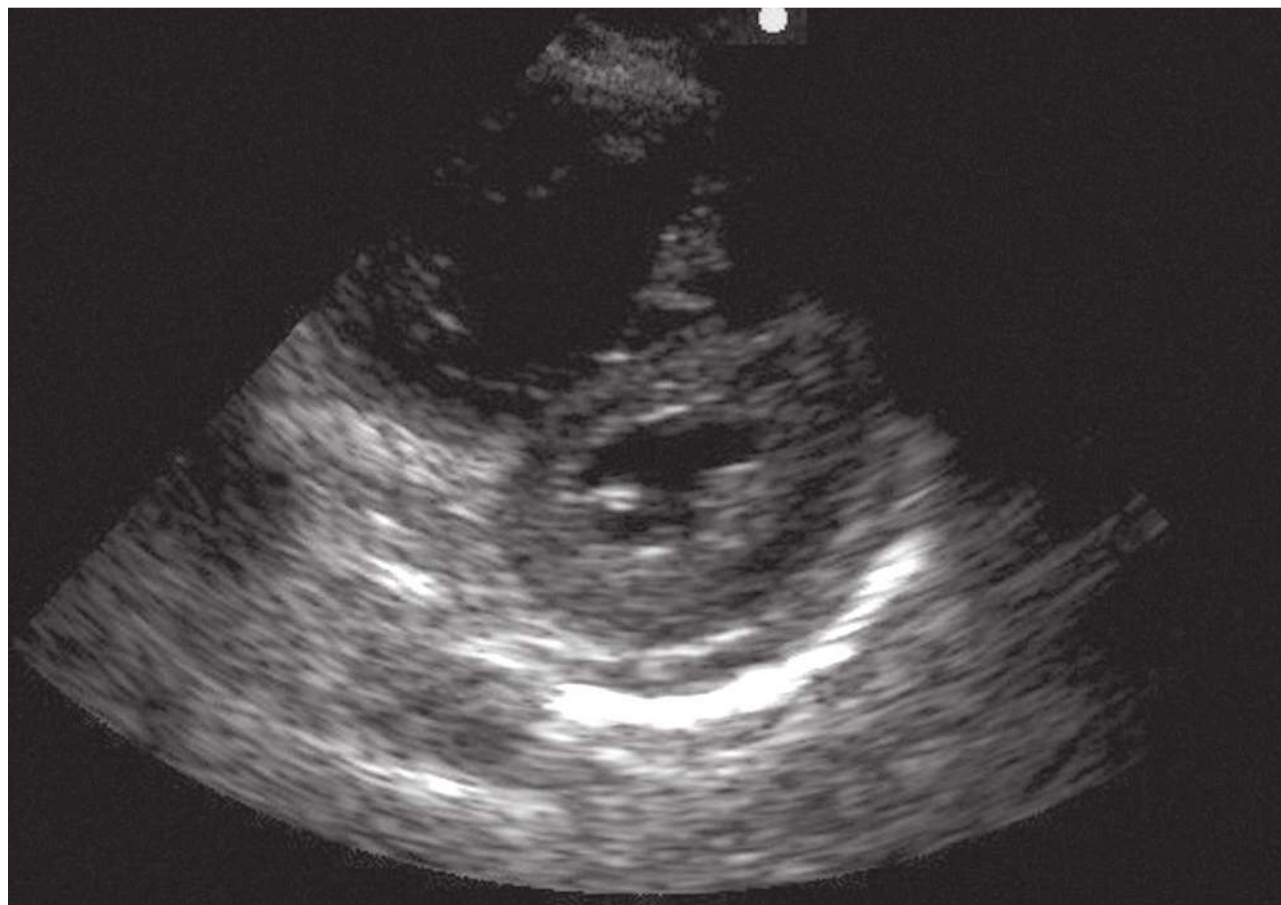


FIGURE 53-50 Parasternal short-axis view showing right ventricular dilation and septal shift. Note the characteristic D sign, with flattening of the septal wall during diastole secondary to increased right ventricular pressure. This gives the left ventricle a D shape, as opposed to its usual rounded O shape.

pump failure. This finding is best seen in the subxiphoid four-chamber or apical four-chamber views. This finding is also known as McConnell's sign, where there is apical contraction and lateral RV wall hypokinesis. In addition, the RV may lose its typical triangular or wedge-shaped appearance and take on more of an ovoid shape.

Measured RV parameters include RV outflow tract diameter and time-velocity integral, RV EDD (basal, midcavity, and longitudinal), RV end-diastolic wall thickness, RV systolic pressure (RVSP), RV-to-LV EDD ratio (RV/LV EDD), right atrial midcavity diameter, and end-systolic area. However, these measurements are time-consuming. An easier quick measurement to assess for RV dysfunction is the tricuspid annular plane systolic excursion (TAPSE).

TAPSE is a well-validated method of assessing RV function based on how much the lateral tricuspid annulus moves vertically during systole. There is decrease in annular displacement with worsening RV function. TAPSE is measured by obtaining an apical four-chamber view with full visualization of the lateral annulus. Using M-mode, the cursor is placed through the lateral tricuspid annulus to obtain an M-mode tracing. The measurement of the vertical displacement of the lateral tricuspid annulus is suggestive of RV function. A TAPSE value of < 1.7 cm is abnormal, and a TAPSE of 0.5 cm is suggestive of severe RV pathology (Figure 53-51).

At this time, there are no established criteria for the objective assessment of RV function in patients with acute PE. However, there are increasing data that show the TAPSE is progressively filling this gap. Tricuspid annular motion was analyzed by calculation of the TAPSE and tricuspid annular systolic velocity (TASV) in patients with PE in a recent study.³⁸ In this study, the authors measured RV systolic function with analysis of tricuspid annular motion in acute PE patients. TAPSE has low interobserver variability and overcomes the limitations of complex RV geometry. The authors

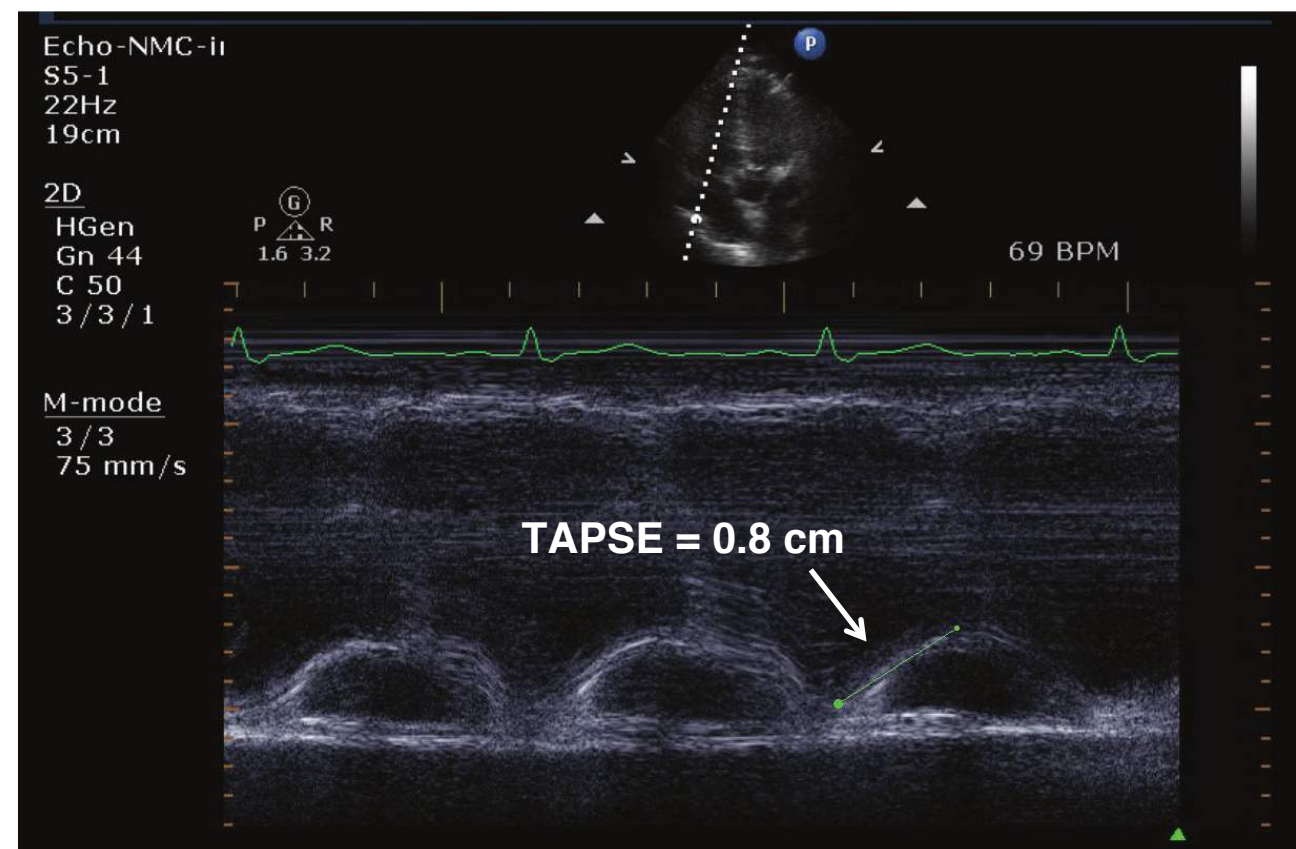


FIGURE 53-51 Measurement of TAPSE through the lateral annulus of the right ventricle using M-Mode in the apical four-chamber view. The TAPSE is 0.8 cm in this patient, demonstrating significant right ventricular dysfunction.

found that the best cutoff of TAPSE for detection of RV systolic dysfunction was 1.75 cm, with a sensitivity of 87% and specificity 91%. The best cutoff for TASV was 13.8 cm/sec, with a sensitivity 86% and specificity 78%. Because, there was no statistical significance in the detection of RV dysfunction (difference = 0.07, 95% CI = -0.21 to 0.17 , $p = 0.130$) between TAPSE and TASV, the emergency physician can simply measure the TAPSE, which is easy to do.

The study concluded that abnormal TAPSE is associated with poor RV systolic function in patients with acute PE and is related to long-term mortality. This may make TAPSE not only a marker of RV function but also a prognostic indicator for long-term survival in patients with PE.

CLOT VISUALIZATION

Occasionally, mobile intracardiac thrombus is directly visualized on echocardiography. This represents a pulmonary embolus in transit and should prompt aggressive treatment (Figures 53-52 and 53-53). The apical four-chamber view is the easiest view to visualize this possible thrombus in situ.

Characteristic ultrasonography findings facilitate early diagnosis as well as provide prognostic information in patients with PE.⁴ These findings need to be interpreted in the context of the clinical picture because similar findings can be seen in COPD, obstructive sleep apnea, pulmonary hypertension, and right-sided myocardial infarction. The relatively poor sensitivity of ultrasound findings necessitates other investigations to rule out the diagnosis of PTE in critically ill patients.

DIFFERENTIATION OF PEA AND SHOCK STATES

Using the techniques illustrated in this chapter, physicians can use echocardiography to differentiate shock states. This is best illustrated in a prospective study that showed using bedside ultrasound improved diagnostic accuracy in medical patients with undifferentiated hypotension.³⁹ The authors conducted a randomized controlled trial enrolling 184 nontrauma

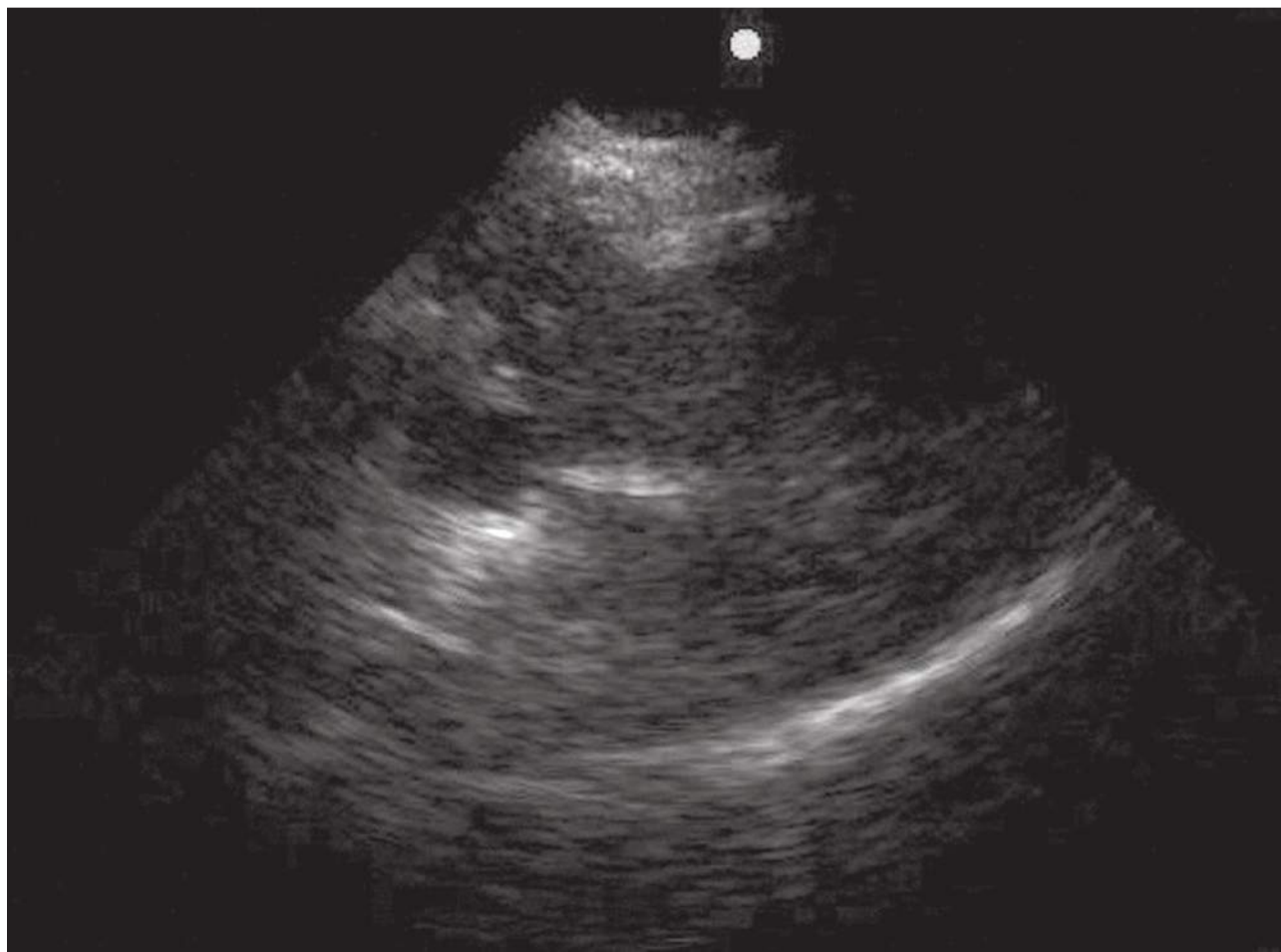


FIGURE 53-52 Subxiphoid four-chamber view showing right ventricular dilation and echogenic clot inside the right ventricle. The clot was seen to be freely mobile in real time and represents a pulmonary embolus in transit. This patient presented in pulseless electrical activity (PEA), was treated with tissue plasminogen activator (TPA), and had return of spontaneous circulation.

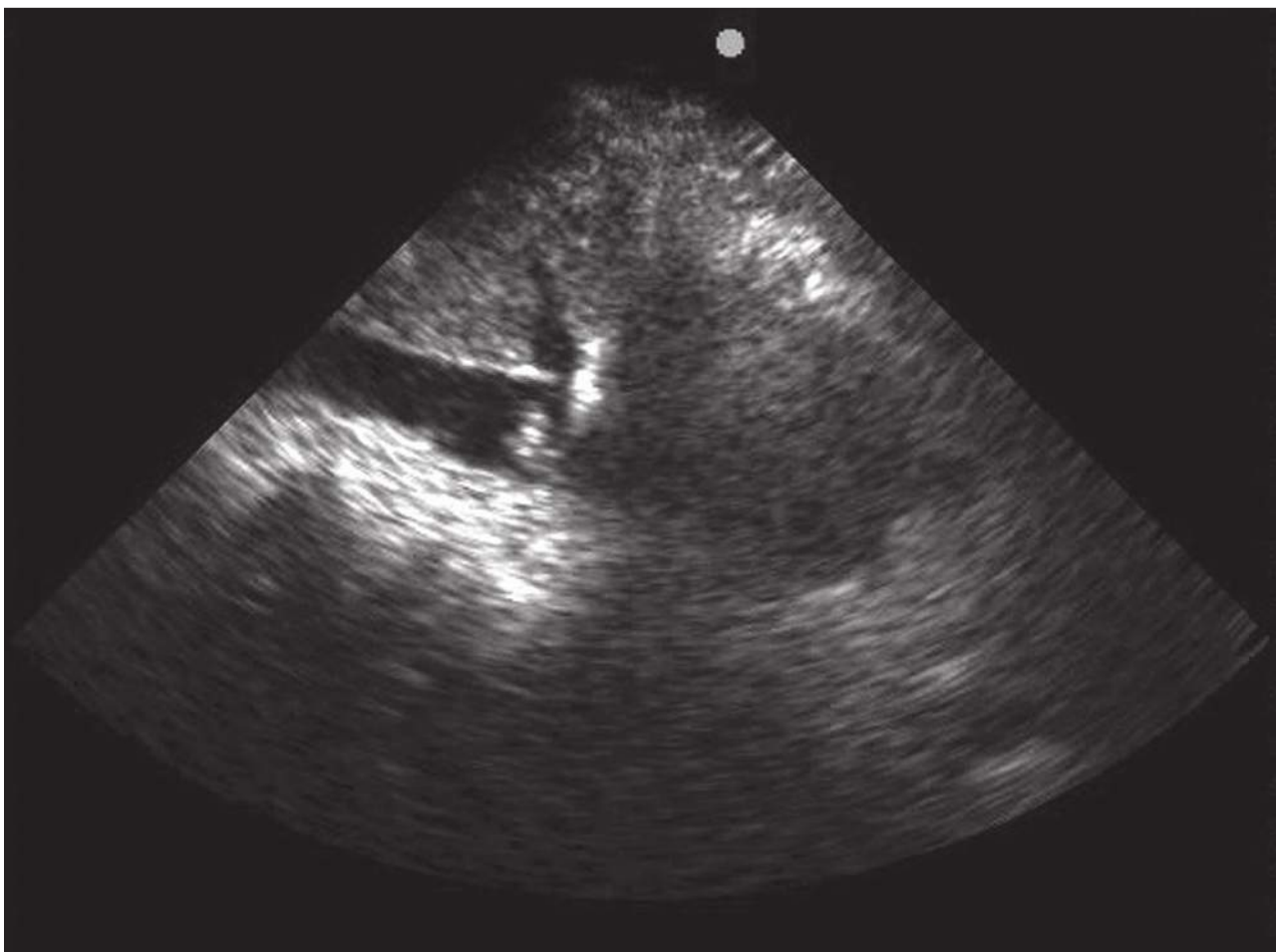


FIGURE 53-53 Subxiphoid inferior vena cava (IVC) view showing an echogenic clot in the IVC at the level of the hepatic vein junction. The clot was seen to be freely mobile in real time, moving between the IVC and right atrium.

patients with hypotension and at least one clinical sign of shock. Patients were randomized to receive an immediate ultrasound exam versus an ultrasound exam delayed by 15–30 minutes. The ultrasound exam consisted of a five-view echocardiogram (parasternal long- and short-axis, apical four-chamber, subxiphoid four-chamber, and IVC views), as

well as a view of the hepatorenal recess to evaluate for free intraperitoneal fluid and a transverse view of the abdominal aorta to evaluate for the presence of an AAA. This exam took less than 5 minutes to complete. At 15 minutes, in the immediate ultrasound group physicians entertained a smaller number of viable diagnoses (median 4 vs. 9, $P < .0001$), and ranked the correct final diagnosis as the most likely one more frequently (80% vs. 50%, difference 30%). This study is a

TABLE 53-2: Rapid Ultrasound in Shock (RUSH) Protocol: Ultrasonographic Findings Seen with Different Shock States

RUSH Evaluation	Cardiogenic Shock	Hypovolemic Shock	Obstructive Shock	Distributive Shock
Pump				
US exams	Hypocontractile heart	Hyperdynamic heart	Hyperdynamic left ventricle	Hyperdynamic heart (sepsis)
Cardiac	Dilated ventricular chamber size	Small ventricular chamber size	Dilated RV (PE, Cor Pulmonale)	Small/normal ventricular chamber size
			Hyperdynamic and collapsible RV with pericardial effusion (tamponade)	
Tank				
IVC	Distended and noncollapsible IVC	Small and collapsible IVC	Distended and noncollapsible IVC	Small/normal IVC
FAST exam	^a (+/- intra-abdominal free fluid)	^a (+/- intra-abdominal free fluid)	^a (+/- intra-abdominal free fluid)	^a (+/- intra-abdominal free fluid)
Lung exam	^a (+/- pleural fluid) Excessive B-lines (pulmonary edema)	^a (+/- pleural fluid)	^a (+/- pleural fluid) Absent lung slide (PTX)	^a (+/- pleural fluid)
Pipes				
Aorta	Normal Aorta	^a (+/- AAA/Aortic dissection)	Normal Aorta	Normal Aorta
Proximal DVT	No DVT	No DVT	DVT	No DVT

^aDepending on shock etiology.
US, ultrasound; RV, right ventricle; PE, pulmonary embolism; IVC, inferior vena cava; PTX, pneumothorax; FAST, focused assessment of sonography in trauma; DVT, deep vein thrombosis.

great example of how to use echocardiography in the critically ill patient and shows how using echocardiography can rapidly hone the differential diagnosis and allow greater certainty when faced with an undifferentiated hypotensive patient.

In 2010, the Rapid Ultrasound in Shock (RUSH) exam was described as a proposed systemic algorithm for evaluation of shock.⁴⁰ This protocol involves a quick three-step bedside sonographic assessment simplified as Step 1: Evaluation of pump, Step 2: Evaluation of tank, Step 3: Evaluation of pipes [Table 53-2]. By focusing on both the anatomy and the physiology, point-of-care ultrasound by the emergency physician may help in differentiating between various etiologies of hypotension in the unstable patient.

CONCLUSION

With relatively brief training, physicians can learn to perform and interpret echocardiography. Using this technology, physicians can rapidly and definitively assess for cardiac activity in cardiac arrest, immediately differentiate treatable causes of PEA and shock, evaluate for pericardial effusion and tamponade, estimate LV systolic function, identify acute right heart strain, noninvasively estimate preload and RV filling pressure, and direct resuscitation and medical decision-making with improved diagnostic accuracy.

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Ultrasound-Guided Critical Care Procedures

Ashika Jain • Lawrence E. Haines • Eitan Dickman

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INTRODUCTION

The use of point-of-care ultrasonography has become an integral tool for evaluating and managing the critically ill patient. Improved image quality and increased portability of ultrasound machines have augmented the utility of physician-performed bedside ultrasonography in the emergency department and the intensive care unit. Not only is ultrasound useful diagnostically, but it can also shine a light into the darkness of invasive procedures traditionally performed with a landmark or “blind” technique. Initially, the ultrasound-guided procedure may take more time as the practitioner’s skills are developing, but the ultimate benefits of fewer complications, less time to completion, and fewer attempts to complete the procedure make this technique worthwhile to master.^{1,2}

Increased utilization of bedside sonography in the critical care arena has generated a large amount of research in the field. This has led to a paradigm shift in the way that procedures are performed at the bedside. Emblematic of this shift is the document released by the Agency for Research and Health Care Quality, *Making Health Care Safer: A Critical Analysis of Patient Safety Practices*, which states that the body of evidence supports the use of ultrasound guidance for placement of central venous catheters (CVCs).³

The performance of multiple critical care procedures may be improved with the addition of sonographic guidance. This chapter provides information about how ultrasound can be used to guide the following invasive procedures: central venous access, arterial line placement, pericardiocentesis, thoracentesis, paracentesis, lumbar puncture, endotracheal tube placement confirmation, and thoracostomy tube placement confirmation.

PROBE SELECTION

There are multiple transducers to choose from when performing a sonographic study. Selecting the correct probe can make the difference between a good image that is helpful and an image that is of poor quality and misleading. As a general rule, the higher the frequency, the better the resolution. The tradeoff is that high-frequency sound waves cannot penetrate as deeply into the tissues of the body as low frequency sound waves. A high-frequency linear transducer is used to image superficial structures and is ideal for sonographic guidance when obtaining vascular access, performing lumbar puncture, and confirming placement of a thoracostomy or endotracheal tube. A curvilinear probe is most often used for evaluating deep structures in the abdomen and pelvis. Because of its



FIGURE 54-1 The three most commonly used probes. On the left is the high-frequency linear probe. In the center is a low-frequency curvilinear probe and to the right is a phased array probe.

lower frequency, this transducer allows for penetration and a deeper field of view but with a relative loss of resolution. The phased array probe is ideal for intercostal imaging since it has a small footprint, a narrow superficial field of view, and a wider deep field of view (Figure 54-1).

SETUP

When performing an ultrasound-guided procedure, the practitioner should position the ultrasound machine in such a way as to allow for easy visibility of the ultrasound screen. The ultrasound machine should be placed alongside the patient's bed directly in line with the operator's line of vision. This allows for minimal eye movement while looking at the ultrasound screen and performing the procedure. The machine should also be placed in a position so that there is enough cord slack to allow for adequate maneuvering of the transducer during the procedure (Figures 54-2 and 54-3).

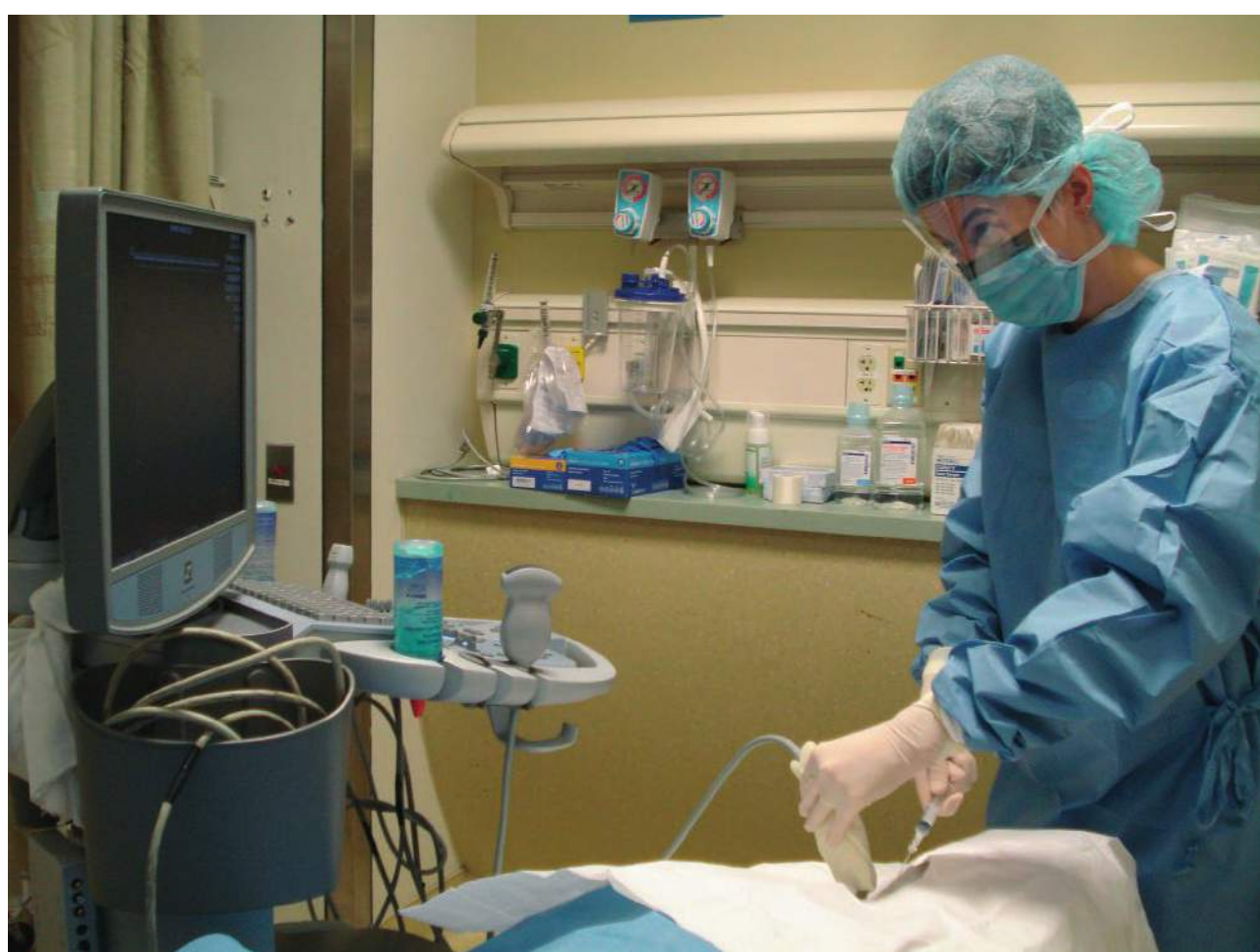


FIGURE 54-2 Optimal relationship between practitioner, patient, and ultrasound machine. Note the machine is in the same line of sight as the patient.

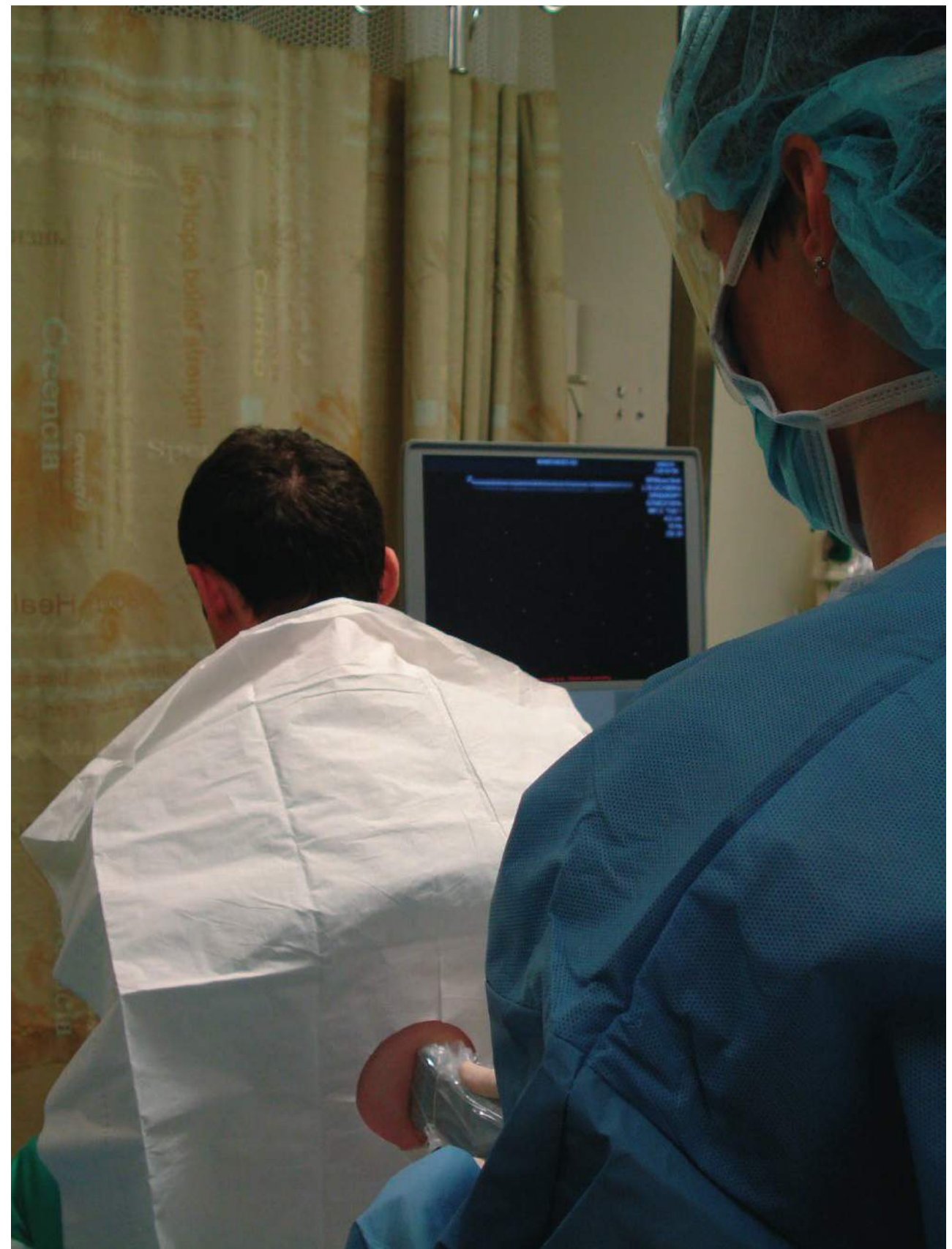


FIGURE 54-3 Note the relationship between patient and ultrasound machine.

STERILITY

When performing any invasive procedure, standard aseptic technique should be observed. Sterile gown, mask, cap, and gloves should be donned for all ultrasound-guided procedures. The addition of the ultrasound probe into the sterile field has the potential to compromise the sterility of the procedure; therefore, sterile transducer covers are essential. A non-sterile conducting medium (gel) can be placed between the probe and the sterile cover, but a sterile conducting medium such as sterile ultrasound gel or sterile surgical lubricating jelly is placed between the probe cover and the skin (Figure 54-4).

DYNAMIC VERSUS STATIC

Ultrasound guidance may be dynamic or static. With dynamic ultrasound guidance, the procedure is performed using continuous imaging. This is strongly recommended for vascular access in order to ensure proper trajectory of the needle during the procedure. With static imaging, the anatomy is sonographically visualized, and the needle entry point is marked on the skin. The transducer is then removed, the area is appropriately cleansed, and the procedure is performed in the traditional manner. The ultrasound probe does not need to be in a sterile sheath when using static imaging. When



FIGURE 54-4 A commercially available sterile probe sheath, which covers the cord as well.

employing static imaging, it is important that the patient not change position once initial imaging has been performed because the needle insertion site or the needle path may need to be altered.

SINGLE- VERSUS TWO-OPERATOR TECHNIQUE

When first learning how to perform ultrasound-guided procedures, a two-person technique may be easier if dynamic ultrasound guidance is utilized. Using this approach, one person holds the transducer and guides the other person who performs the procedure. Once proficiency is obtained, a single-person technique can be employed, in which the transducer is held in the nondominant hand and the needle is held in the dominant hand.

CENTRAL VENOUS ACCESS

Central venous access is frequently necessary in the management of the critically ill patient. More than 5 million CVCs are placed annually by physicians.^{4,5} CVCs allow measurement of hemodynamic variables that cannot be assessed accurately by noninvasive means and allow delivery of medications and nutritional support that cannot be given safely through peripheral intravenous catheters. Other indications for central venous access include lack of peripheral access and the need for aggressive fluid resuscitation. Many factors can make obtaining central venous access more difficult including body habitus, hypovolemia, anatomical anomalies, multiple previous cannulations of these vessels due to complications of diabetes and sickle cell disease, intravenous drug use, and the presence of indwelling catheters.⁶ Typical sites for central venous access are the internal jugular vein, the supraclavicular and infraclavicular approaches to the subclavian vein, and the femoral vein.

Mechanical complications (e.g., arterial puncture, hematoma, pneumothorax, and hemothorax) are reported to occur in 5–19% of patients, whereas infectious complications (catheter colonization and associated blood stream infections) transpire in 5–26%, and thrombotic complications (deep venous thrombosis) develop in 2–26% of patients who have a CVC.^{7–10} Furthermore, coagulopathy, anatomic anomalies, anatomic deformity due to trauma, and operator inexperience can all contribute to a failure to cannulate a central vein. When compared with a traditional landmark approach, the use of ultrasound guidance has been shown to significantly reduce mechanical complications^{11–13} without increasing the risk of infection.¹⁴ In a review of the literature, CVC placement under ultrasound guidance was shown to decrease placement failure by 64%, complications by 78%, and multiple placement attempts by 40%.¹⁵ This effect was even more pronounced in inexperienced operators.¹⁶ Another study demonstrated that inexperienced operators had fewer complications with the use of ultrasound than with landmark technique (7.8% vs. 24%).¹⁷ The institution of an ultrasound training program within an emergency medicine residency program has been associated with lower mechanical complication rates from CVC placement when compared to a time period directly prior to initiation of the ultrasound training program.¹⁸ In a recent Cochrane review, it was concluded that ultrasound guidance reduced complications in all of the locations commonly used for CVC placement.^{19,20} Ultrasound guidance has also been shown to increase the success rates of placement of CVCs in patients seen in a pediatric emergency department.²¹ The overwhelming body of evidence supports the use of sonographic guidance when placing a CVC.

As discussed earlier, appropriate positioning of the patient and the ultrasound machine is crucial for success. When attempting to cannulate the internal jugular or the subclavian vein, placing the patient in the Trendelenburg position will help to engorge the vein of interest and will allow for easier sonographic visualization and better blood return once the vein is punctured. For the femoral vein, reverse Trendelenburg will assist in this regard. Humming has been shown to be as effective as the Valsalva maneuver and Trendelenburg position for ultrasonographic visualization of the internal jugular vein and common femoral vein.²²

Using a high-frequency linear array transducer, the area of interest should be imaged prior to the procedure to identify all pertinent structures as well as any structures in the field that should be avoided. In addition, confirmation that the desired vein is easily compressible demonstrates lack of an occult venous thrombosis. Recognizing the difference between the artery and the vein is extremely important in order to avoid arterial puncture. Veins are more easily compressible and have thinner walls than arteries. Doppler can be employed if there is doubt. Arteries will demonstrate characteristic arterial pulsations, whereas veins will demonstrate respirophasic flow.

For the short-axis (transverse) approach, the depth of the center of the vessel from the skin surface should be measured. Once the depth is ascertained, the same distance is measured

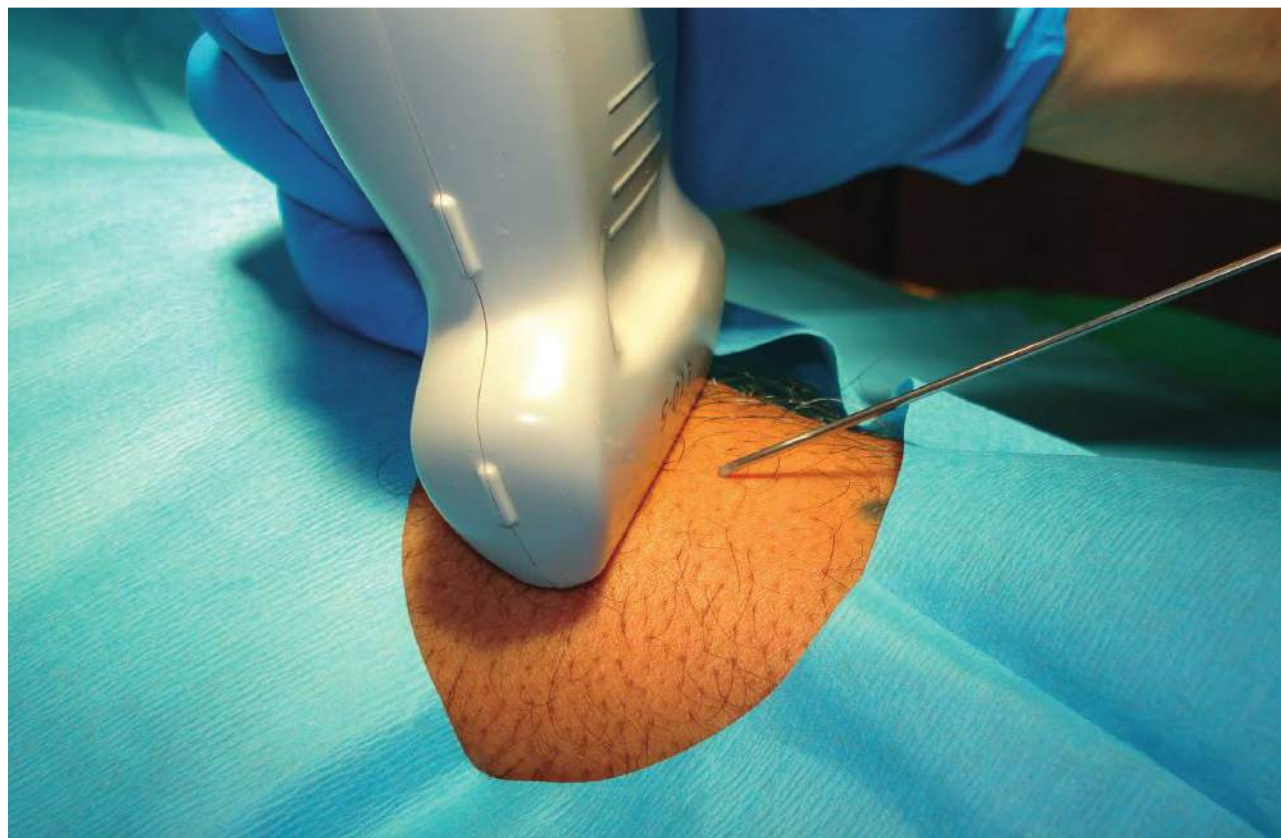


FIGURE 54-5 Needle–probe relationship in short axis.

from the middle of the probe on the skin surface, with the needle entering cephalad to the probe when cannulating the internal jugular vein and caudad to the transducer when accessing the femoral vein. This is where the needle should enter at a 45-degree angle. By triangulation, the needle tip should pierce the vessel wall and end up in the middle of the vessel. The needle is introduced into the ultrasound field under the center of the long face of the probe and is seen as a hyperechoic dot in cross-section. The true depth of the needle may be difficult to appreciate when using a transverse orientation. The transducer may need to be moved in a caudal or cephalad direction in order to find the needle tip. There are multiple visualization techniques that can be utilized to monitor needle placement and movement. The practitioner must be cognizant of the needle tip at all times during this procedure. Otherwise, there is a risk of the needle puncturing a nearby critical structure that is not the intended target (Figures 54-5 to 54-8).^{2,11}

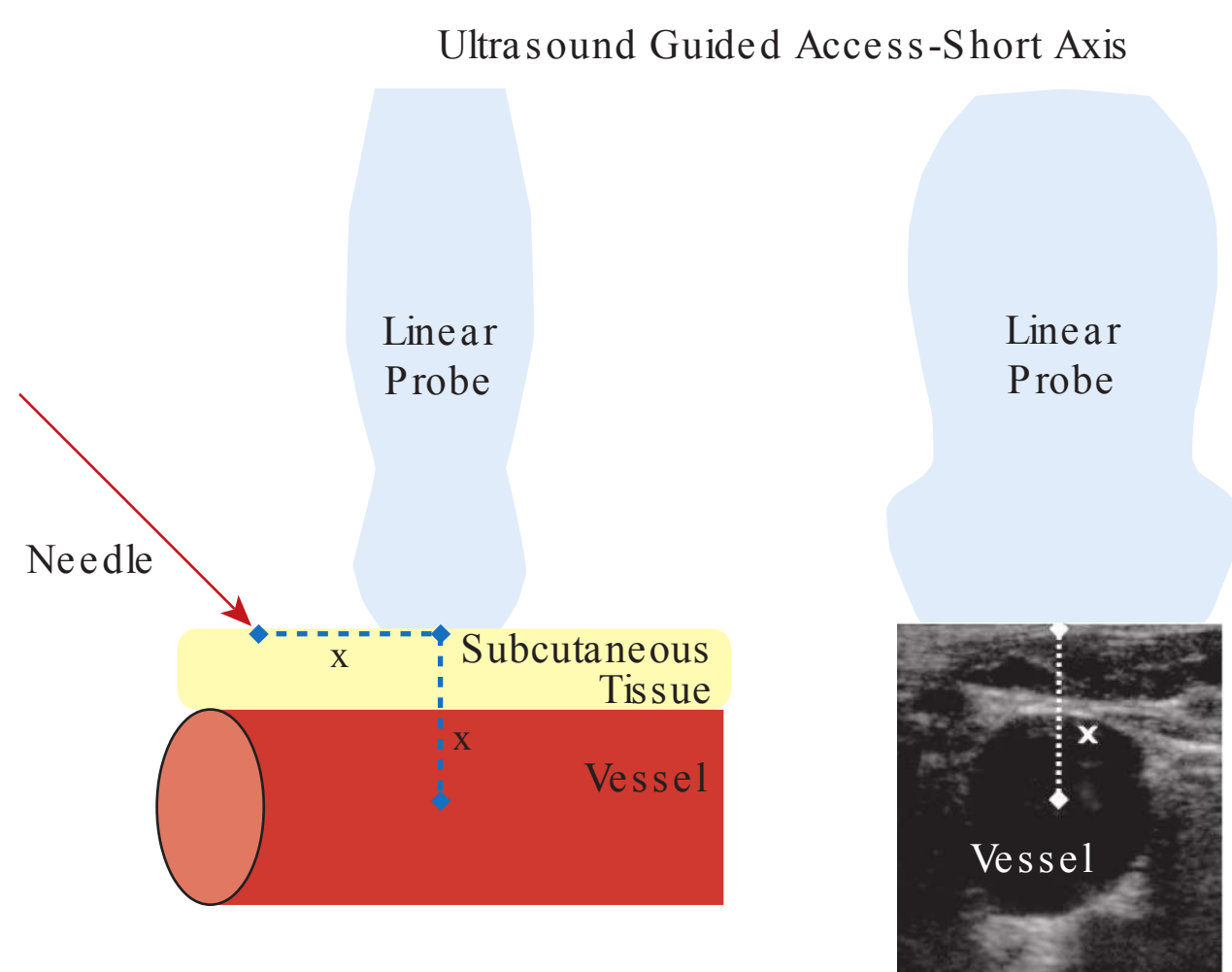


FIGURE 54-6 Short-axis schematic. The distance from the center of the target vessel to the skin surface is measured. This same distance is measured back from the middle of the transducer, and this is where the needle should penetrate the skin at a 45-degree angle.

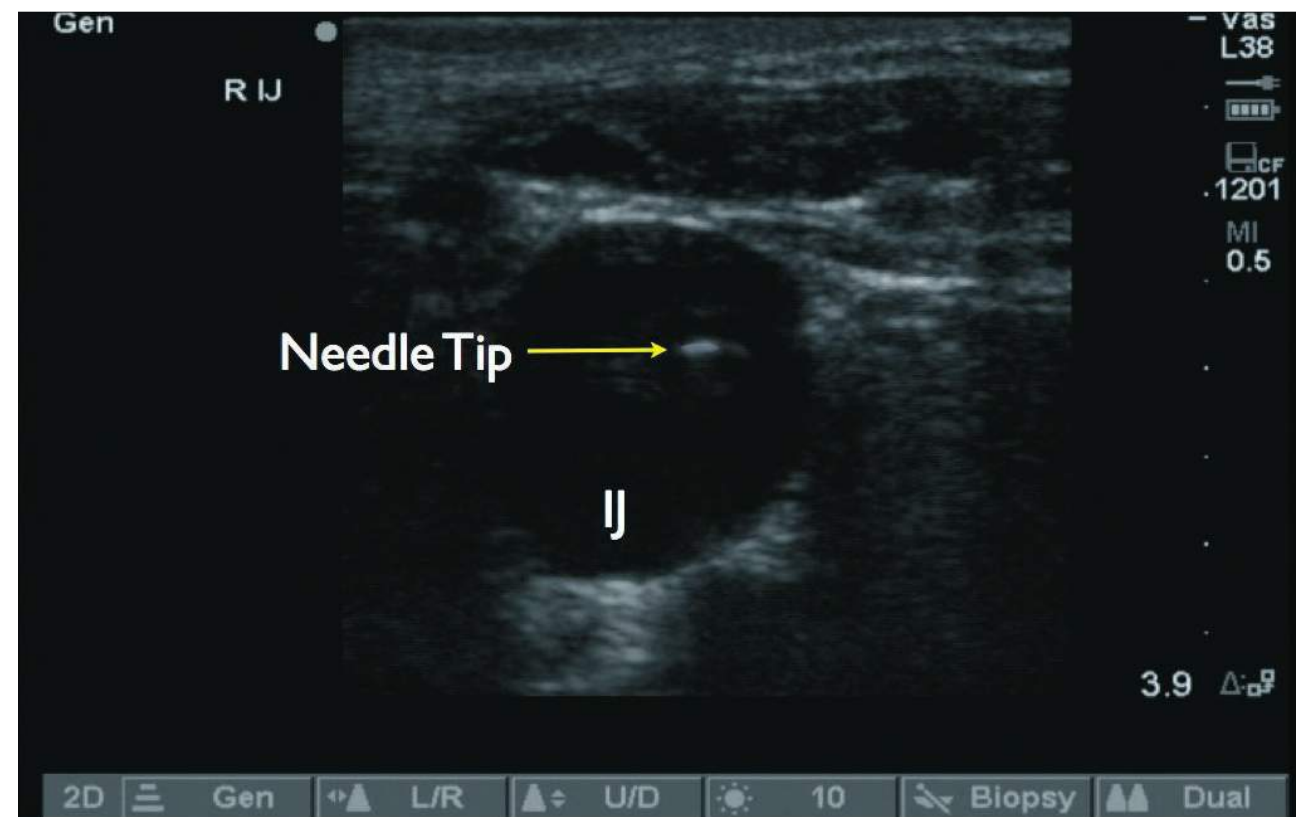


FIGURE 54-7 Needle tip in the right internal jugular vein (IJ) in short-axis view.

For the longitudinal approach, the needle is introduced in the same plane as the long axis of the ultrasound transducer. The entire length and the depth of the needle are appreciated using this technique. The needle must be kept directly under the center of the transducer because there will be complete loss of visualization of the needle if either the needle or the transducer is moved out of plane.²³ This is because the width of the beam generated by the transducer is very narrow. Keeping the needle in plane can be technically challenging, but evidence supports the use of the longitudinal approach over the transverse approach because it is associated with lower rates of posterior wall puncture rates when attempting to cannulate the internal jugular vein²⁴ (Figures 54-9 to 54-11), as well as decreased time to cannulation and decreased number of redirections when compared to a short axis approach.²⁵

Once access has been established, confirmation of correct catheter placement and depth are crucial to ensure safe infusion of potentially caustic medications. Currently, a chest radiograph is used to confirm proper placement and also to evaluate for pneumothorax. However, obtaining a radiograph can lead to delay in catheter utilization. Performing a bedside lung ultrasound to evaluate for lung sliding has been shown

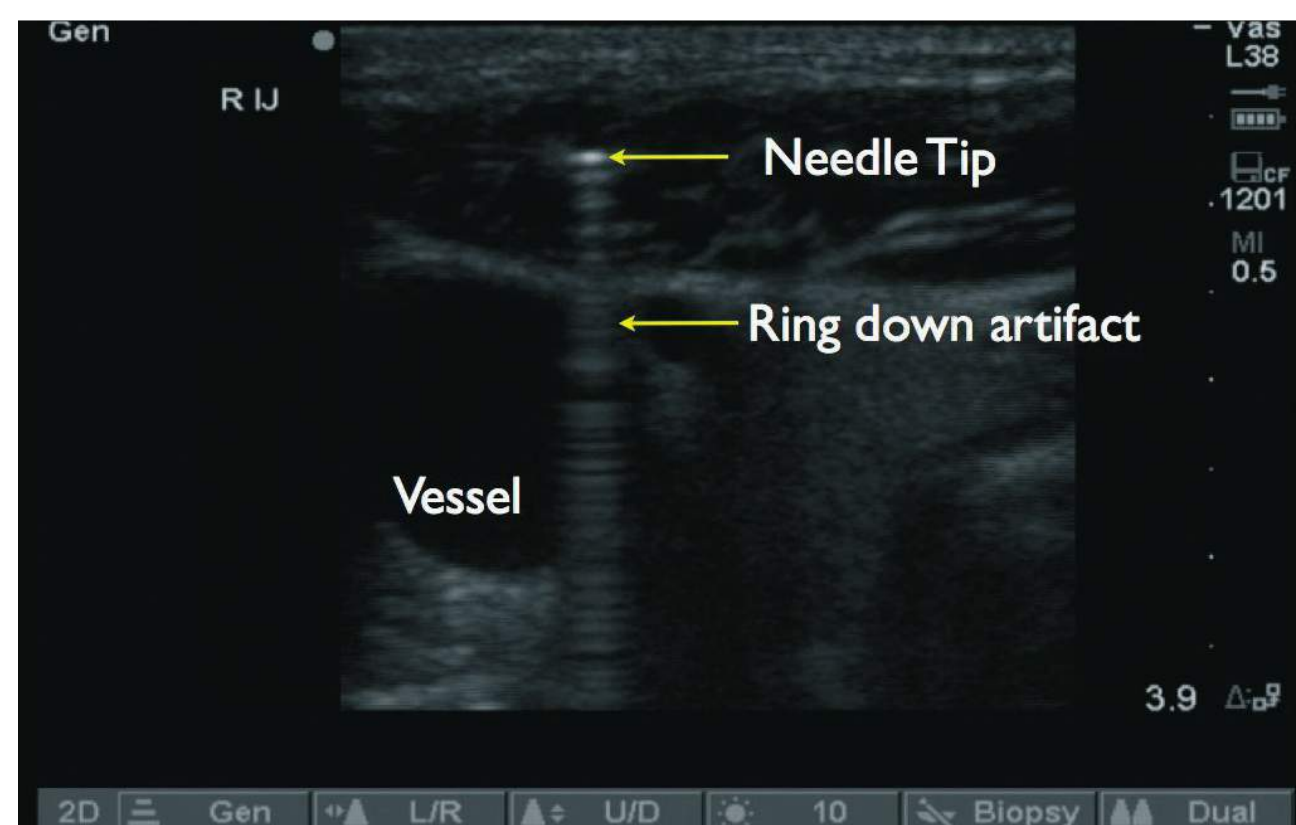


FIGURE 54-8 Ring-down artifact seen in a short-axis view of a needle near the right internal jugular vein.



FIGURE 54-9 Needle–probe relationship in long axis.

to be more sensitive than a portable chest radiograph for the detection of pneumothorax.^{26,27}

In addition to detecting pneumothorax, ultrasonography can be used to confirm proper location of the catheter through the use of a bubble test.²⁸ Once the catheter has been placed, 10 mL of saline is rapidly flushed into the CVC while the right atrium is visualized with a subxiphoid view. A “snow storm” appearance, representing turbulent flow, should be visualized within 2 seconds of the flush to confirm placement at or very near the right atrium.^{29–31} It has been shown that a combination of these ultrasounds can confirm both CVC placement and the presence or absence of pneumothorax in significantly shorter time than chest x-ray.³²

Internal Jugular Vein

The internal jugular vein lies deep to the sternocleidomastoid muscle and is usually lateral and superficial to the carotid artery. Placing a catheter in this vein allows for central venous pressure monitoring and has the advantage of lower rates of pneumothorax when compared with attempting to cannulate the subclavian vein.⁵ In addition, catheters in the internal jugular vein have a lower infection rate than catheters in the femoral vein.³³

For this procedure, place the patient in the Trendelenburg position. The ultrasound machine is positioned next to

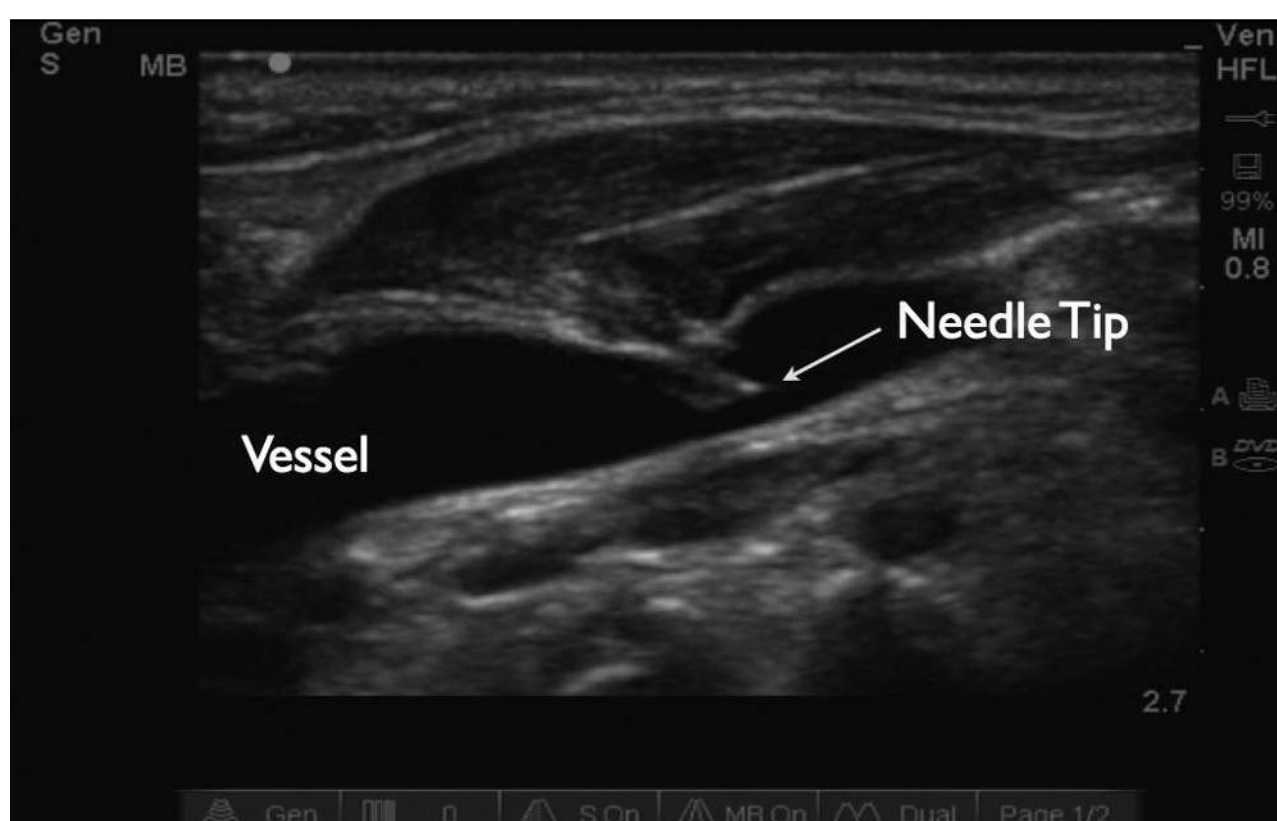


FIGURE 54-10 Longitudinal view of needle entering vessel.

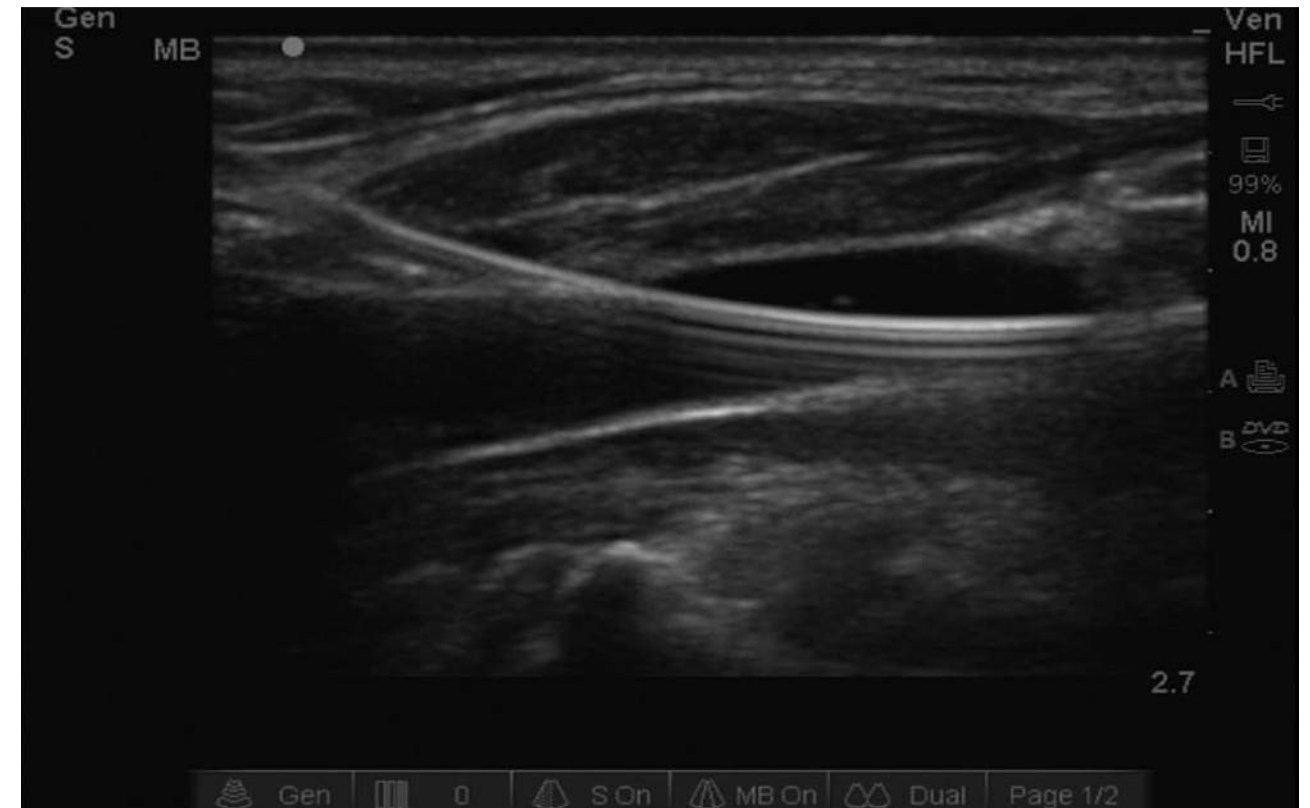


FIGURE 54-11 Longitudinal view of a guide wire being introduced into the vessel. Note ring-down artifact from the guidewire.

the patient’s bed, with the screen facing the head of the bed. With the probe, it is best to visualize an area where the carotid artery and the internal jugular vein are not in the same vertical plane. This will minimize the chance of inadvertent arterial puncture via the posterior venous wall.^{12,15,34,35} Once the vessel is visualized and the surrounding anatomy appreciated, vessel cannulation proceeds as described earlier, although an attempt should be made to avoid cannulating the internal jugular vein when it is positioned directly anterior to the carotid artery (Figure 54-12). In most instances, moving the probe superiorly or inferiorly will reveal an area where there is greater separation of these two vessels. There is evidence to support the use of a “bevel down” approach when performing the venipuncture because it is associated with a lower incidence of hematoma formation than the “bevel up” approach.³⁶

Subclavian Vein

When compared with other possible sites for central venous catheterization, the subclavian vein has the lowest rates of

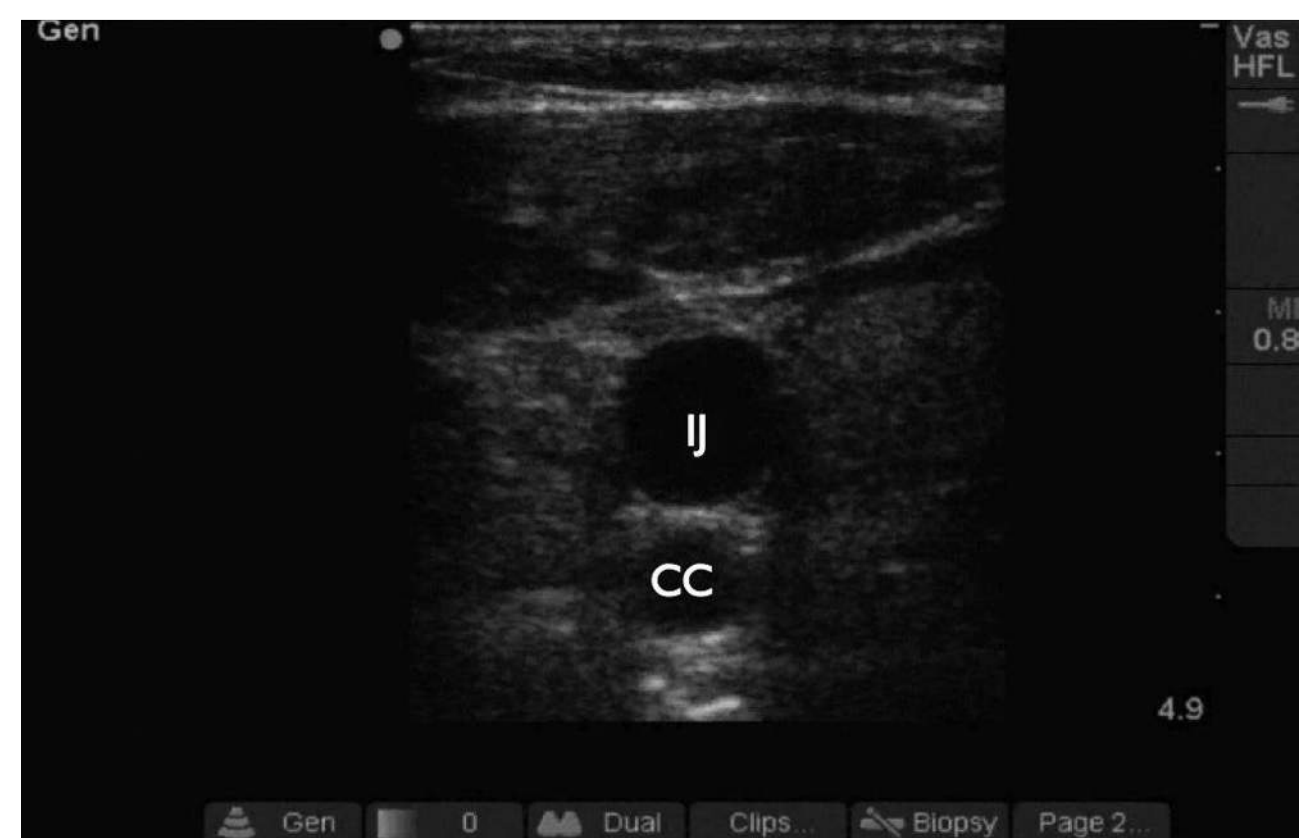


FIGURE 54-12 Example of a poor location for ultrasound-guided central venous access. The internal jugular vein (IJ) is positioned directly over the common carotid artery (CC), which increases the potential for arterial puncture during the procedure.

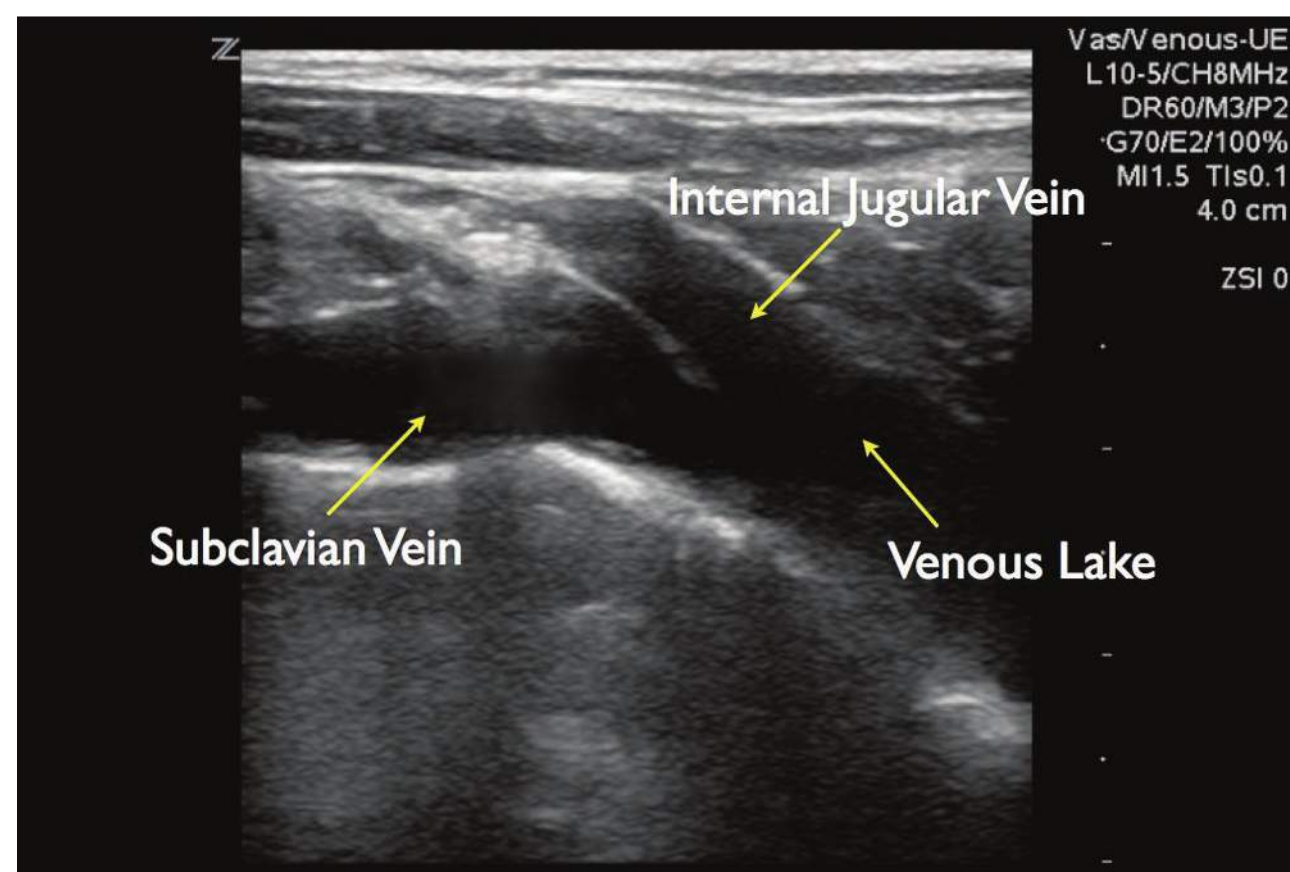


FIGURE 54-13 Longitudinal view of supraclavicular approach for subclavian vein access. Venous lake formed by confluence of internal jugular vein and subclavian vein.

infection but also the highest rates of pneumothorax.^{5,37} For this procedure, the ultrasound machine should be positioned on the side of the bed opposite to the subclavian vein that will be cannulated. This will allow for easy visualization of the screen while placing the catheter. When compared with a landmark approach, there was an increased success rate in patients who had sonographic guidance of subclavian cannulation while time to access and number of attempts were significantly reduced.³⁸ In addition, there is decreased risk of “pinch-off syndrome,” in which the catheter is compressed between the clavicle and the first rib, when the catheter is placed with ultrasound guidance. This is presumably due to the more lateral placement when using ultrasound guidance.³⁹

The subclavian vein crosses under the clavicle just medial to the midclavicular point. It is often difficult to visualize the subclavian vein at this location due to the strong echogenicity and posterior shadowing of the clavicle. To avoid this, one must visualize the vein more proximally or more distally with respect to the clavicle. It is possible to visualize the “venous lake” where the subclavian vein joins the internal jugular vein using the supraclavicular approach. It is also possible to visualize the subclavian vein inferior and lateral to the first rib, where it is referred to as the *proximal axillary vein* (Figures 54-13 and 54-14). The vein may be cannulated in either of these locations. Due to the proximity of the subclavian vein to the lung pleura, a longitudinal approach is advised so that the entire needle can be visualized throughout the procedure.

Femoral Vein

Routine use of the femoral vein for CVC placement should be avoided in adults due to higher rates of infection and deep venous thrombosis formation when compared with other sites.^{5,8,40} However, the femoral vein is readily accessible in an emergent situation and can be useful as a compressible site in the setting of coagulopathy.⁵ It has recently been shown that the success rate of placement of the CVC in the femoral vein is higher when performed with ultrasound guidance.⁴¹

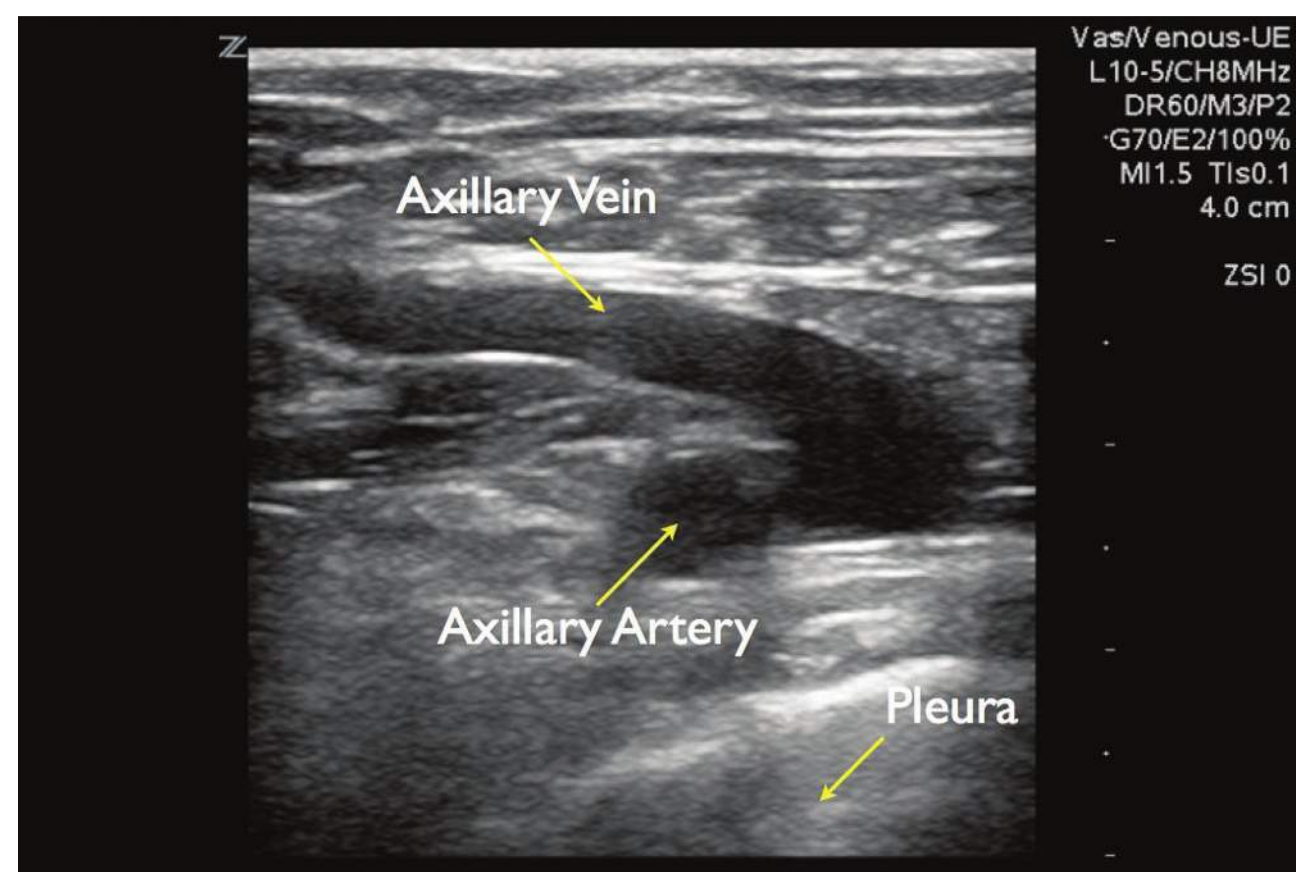


FIGURE 54-14 Longitudinal view of lateral subclavian/axillary vein approach.

To optimize positioning, the patient should be placed in the reverse Trendelenburg position, with the leg externally rotated at the hip to increase the diameter of the femoral vein.⁴² The ultrasound machine should be placed at the side of the bed at shoulder level, with the screen facing toward the patient’s feet. Beginning the procedure in a transverse orientation just inferior to the inguinal ligament allows both the artery and vein to be visualized (Figure 54-15). The area where the greater saphenous vein drains into the common femoral vein usually provides the largest target. Usually, the vein will lie medial to the artery. In the proximal femoral region, the vein and artery lie in the same horizontal plane, whereas, more distally, the vein will be deep to the artery. Find the location where the artery and vein lie next to each other to lessen the chance of inadvertent arterial puncture (Figure 54-15).⁴³

PERIPHERAL INTRAVENOUS ACCESS

Peripheral intravenous access is routinely performed to obtain blood for diagnostic tests as well as for the administration of fluids and medications. There are many factors that can make obtaining intravenous access challenging including obesity, intravenous drug use, and multiple previous peripheral access attempts.^{44,45} Ultrasound-guided peripheral vascular access is safe and rapid and provides an alternative to either central venous access or multiple “blind” attempts.^{46,47} Furthermore, obtaining peripheral intravenous access with sonographic guidance is not associated with an increased risk of infection.⁴⁸ Studies have demonstrated that ultrasound-guided peripheral catheter placement can lead to reduction in the need for CVCs.^{49,50} This procedure has been successfully performed by nursing staff⁵¹ and has the potential to save patients from the complications, discomfort, and costs associated with central venous catheterization.

The high-frequency linear array transducer is utilized for obtaining vascular access of the superficial veins. Veins are round or oval anechoic structures that are easily collapsible

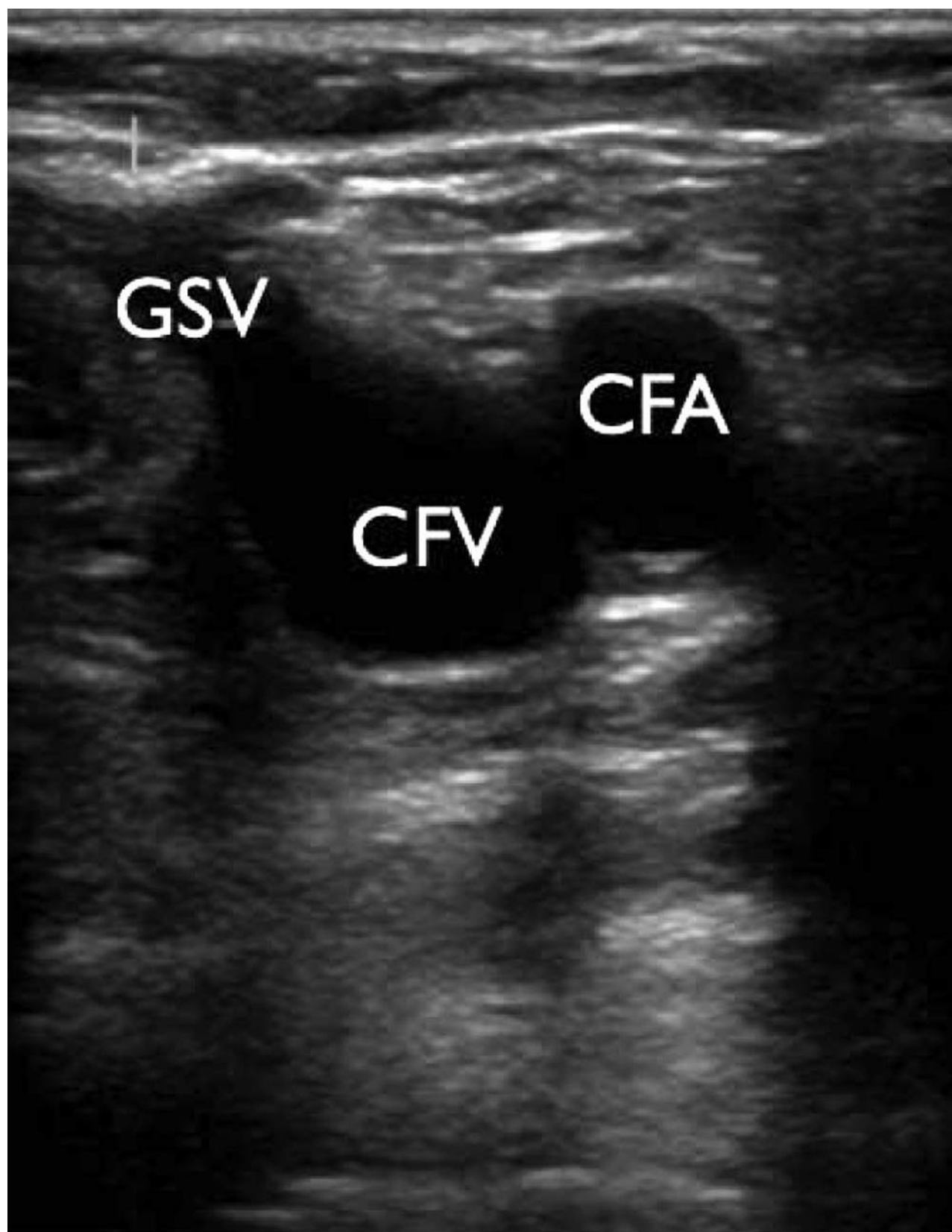


FIGURE 54-15 Transverse image of femoral vessels. CFV is the common femoral vein, CFA is the common femoral artery, and GSV is the greater saphenous vein.

with slight pressure of the probe on the skin. Color Doppler can be utilized to aid in differentiating an artery from a vein. A standard tourniquet should be applied proximal to the site of venipuncture, and the skin should be appropriately cleansed. Once a suitable vein is identified, the static or dynamic technique employing either the in-plane or out-of-plane approach can be used to cannulate the vessel. Frequently, by the time ultrasound is brought to the bedside, the patient has already undergone multiple attempts at vascular access. As a result, the external jugular vein and the veins in the proximal arm are often utilized to gain vascular access. If the brachial or the cephalic veins are cannulated, it is advisable to use a longer (e.g., 2.25-inch) catheter because these veins may be beyond the reach of a standard intravenous catheter (Figures 54-16 and 54-17). This should reduce the risk of infiltration of the surrounding tissue.^{51,52}

Midline Catheter

In the critical care setting, the need for intermediate and long-term access often arises. In instances where prolonged intravenously administered medications are indicated, a midline catheter can be utilized. Midline catheters have been shown to decrease the risk of central line associated blood stream infections (CLABSI).⁵³ The basilic or cephalic veins

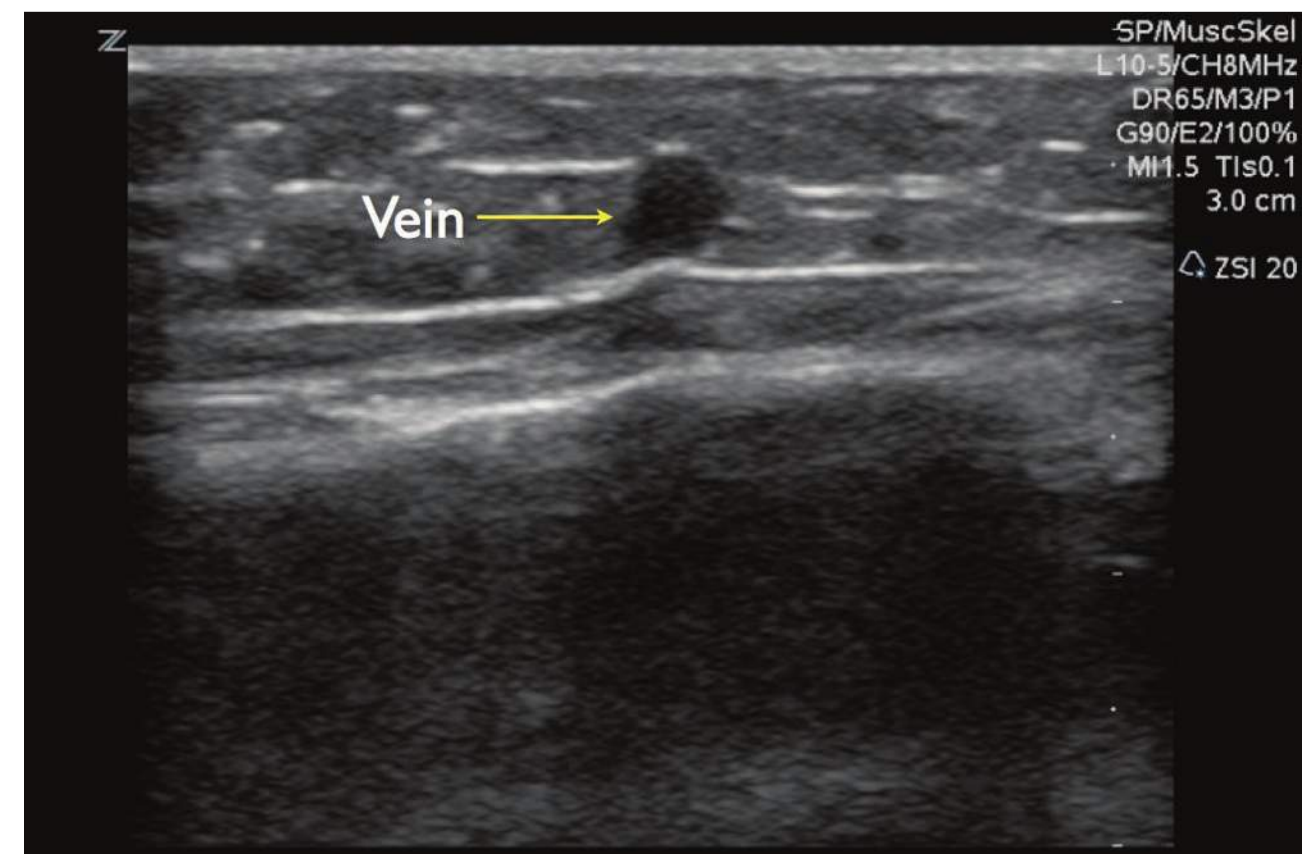


FIGURE 54-16 Short-axis view of a peripheral vein.

are most often utilized. With ultrasound guidance, time to cannulation and complications can both be reduced. Additionally, midline catheters have been shown to be cost effective because trained physician and non-physician ICU staff can place them at a fraction of the cost of a CVC.⁵³

ARTERIAL CATHETER PLACEMENT

Arterial catheter placement in a peripheral artery can be challenging, especially in a hypotensive patient with a weak or absent peripheral pulse. In the intensive care unit, the need for continuous blood pressure monitoring and frequent sampling of arterial blood gas can make these catheters crucial to patient care. Traditionally, the arterial catheter is inserted via a technique using palpation of the pulse to guide the needle insertion. Difficulty with locating the artery or with inserting the catheter subjects patients to multiple painful attempts. The use of ultrasound for arterial catheter insertion has been shown to increase first-pass success, thereby reducing time to insertion and the number of attempts.⁵⁴⁻⁵⁶ It has also been

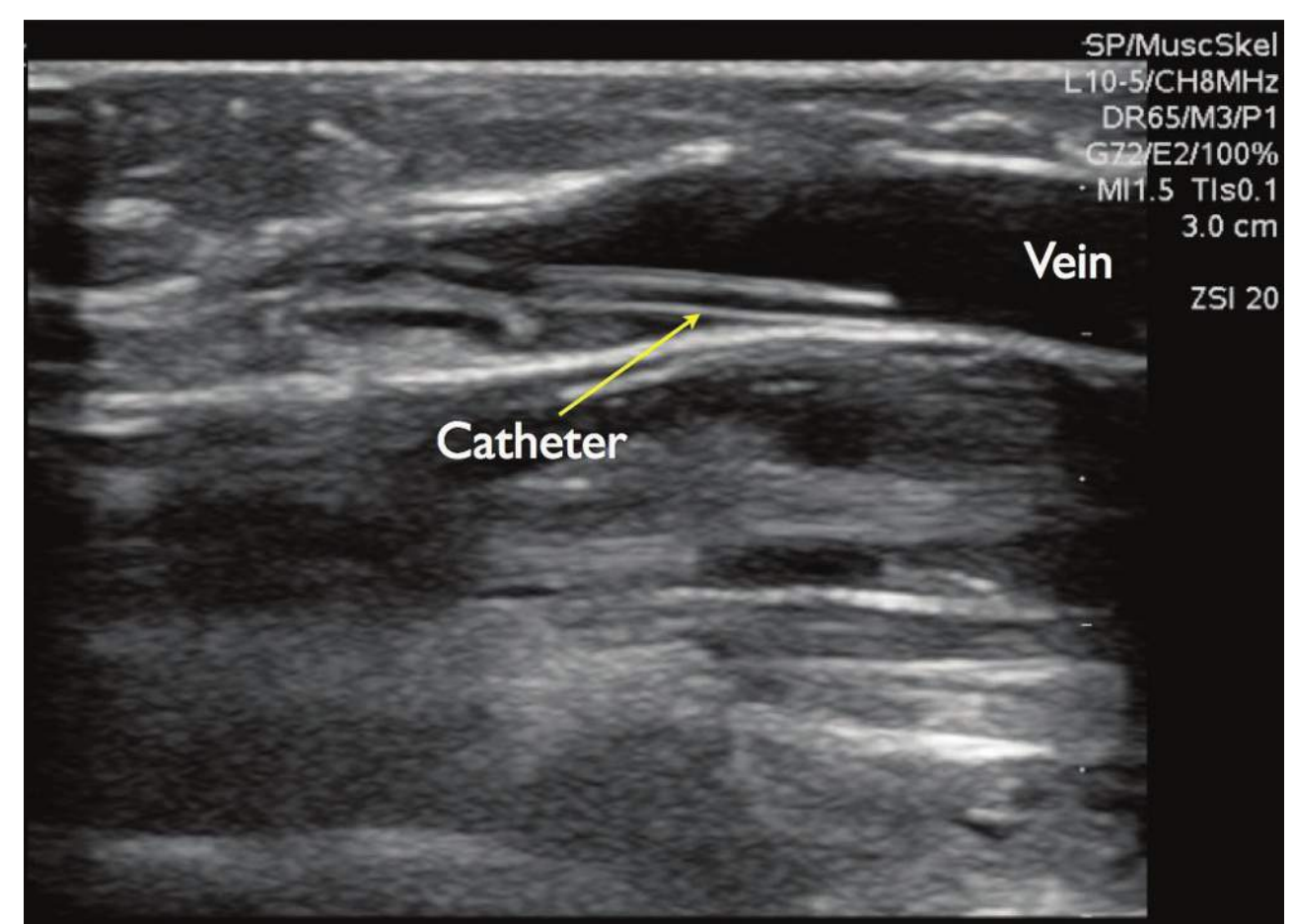


FIGURE 54-17 Longitudinal view of a catheter within a peripheral vein.

shown that respiratory therapists can be successfully taught this technique.⁵⁷

The linear high-frequency ultrasound transducer is used to identify the thick-walled pulsatile artery that is less compressible than the adjacent thin-walled and easily compressible veins. The addition of pulsed wave or color Doppler can be used to visualize the characteristic pulsatile arterial blood flow. For the radial artery, the patients' wrist should be placed in 45 degrees of extension.⁵⁸ The in-plane approach is preferred over the out-of-plane approach.⁵⁹ Once the artery is identified, the catheter can be placed dynamically to monitor first the needle and then the guide wire entering the artery in real time. In cases where the radial artery cannot be cannulated, ultrasound guidance can also be used to cannulate the brachial, femoral, dorsalis pedis, or axillary arteries.^{60,61}

PERICARDIOCENTESIS

Cardiac tamponade is a life-threatening condition that can be temporarily relieved or even remedied with pericardiocentesis. Traditionally, pericardial effusion and tamponade were diagnosed clinically using Beck's triad (hypotension, muffled heart sounds, and jugular venous distention), along with pulsus paradoxus, and a pericardial friction rub. However, many of these findings either occur late in the disease process or may be difficult to appreciate. Echocardiography has become the standard method to diagnose a pericardial effusion and tamponade, and can also be used to localize the area with the largest fluid collection in anticipation of pericardiocentesis.⁶² Emergent pericardiocentesis should be performed when the patient sustains cardiac arrest or hemodynamic instability in the setting of a large pericardial effusion. Major complications of pericardiocentesis include cardiac chamber laceration, intercostal vessel injury, pneumothorax, sustained ventricular tachycardia, and death.^{63,64} Ultrasound guidance can make this potentially dangerous yet life-saving procedure significantly safer.⁶³

The patient should first be imaged using standard cardiac windows with a phased array transducer. This also allows for evaluation of global cardiac function. Tamponade physiology can be diagnosed on ultrasound by confirming the presence of a significant pericardial effusion and by observing right ventricular collapse during early diastole or invagination of the free wall of the right atrium during end diastole. A plethoric inferior vena cava with little change in diameter during respiration as well as alterations in trans-valvular flow velocities with respiration may also be visualized (Figure 54-18).⁶⁵

The subxiphoid and the parasternal approaches are most commonly used for pericardiocentesis. The decision to use one rather than the other lies mainly with operator experience and where the largest amount of fluid is visualized (Figure 54-19).

For a parasternal approach, the patient can be supine, with the upper body elevated 30–45 degrees, or the patient can be placed in the left lateral decubitus position. The patient should be prepped and draped using standard sterile technique. The ultrasound transducer can then be placed in the parasternal

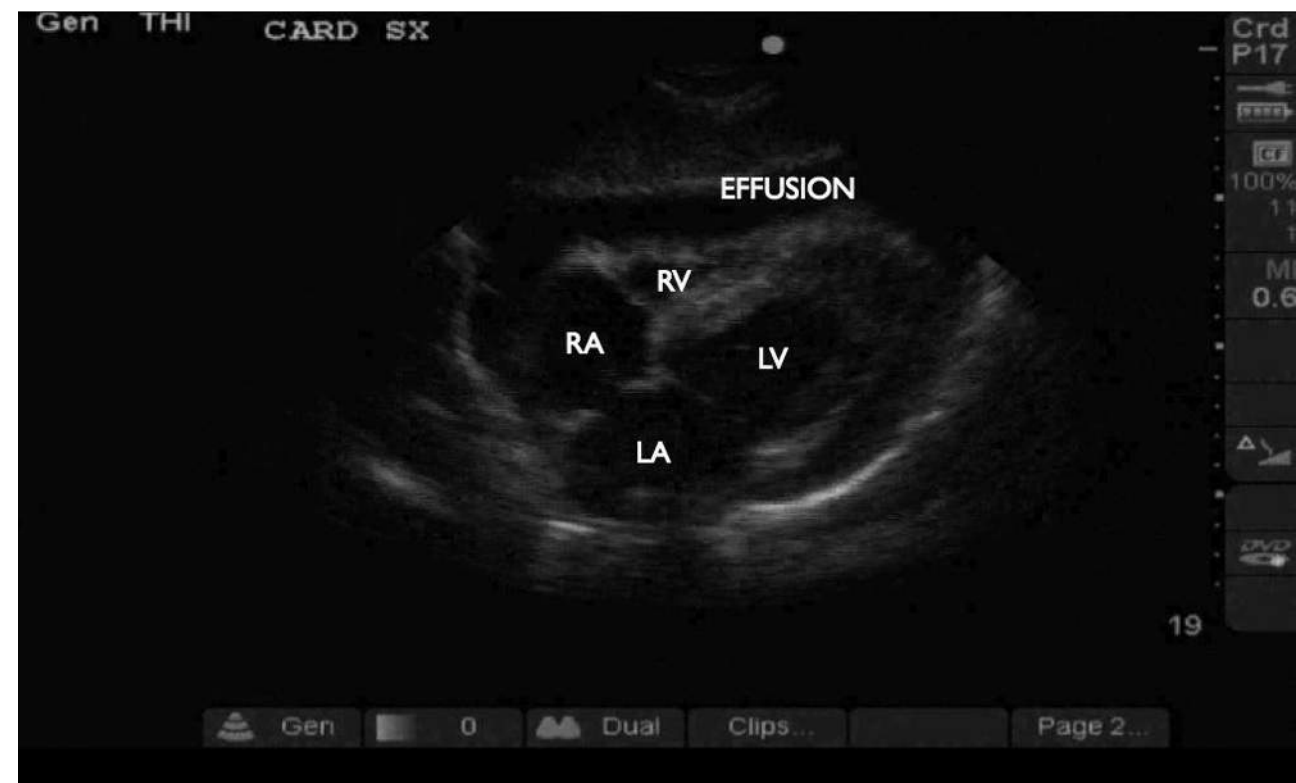


FIGURE 54-18 Tamponade. Subxiphoid view of pericardial effusion with collapse of the right ventricle. RA, right atrium; RV, right ventricle; LA, left atrium; LV, left ventricle.

long-axis orientation at the third or fourth intercostal space just to the left of the sternum to visualize the largest pocket of fluid, which is usually between the probe and the anterior wall of the heart. The distance from the skin to the pericardial space should be measured to judge how far the needle will be advanced in order to enter the pericardial space.⁶⁶ Care must be taken to avoid the left internal mammary artery that lies 3–5 cm lateral to the sternal border. Once the ideal entry path has been determined, local anesthesia should be infiltrated at the entry site and along the proposed path for the needle. The longitudinal approach is recommended for this procedure so that the needle can be visualized throughout the procedure.⁶⁷ The needle should be large bore, 18 gauge or greater, and preferably sheathed with a Teflon catheter to allow for continuous drainage of the effusion. As the needle is inserted, the tip should be followed carefully with continuous sonographic visualization. Once a “flash” of fluid is obtained, the fluid can then be aspirated. If using a catheter, the needle can be advanced a few additional millimeters and the Teflon sheath can be advanced while the needle is removed for continuous drainage.⁶⁸ A small amount of agitated saline can be infused through the needle or the catheter to confirm proper

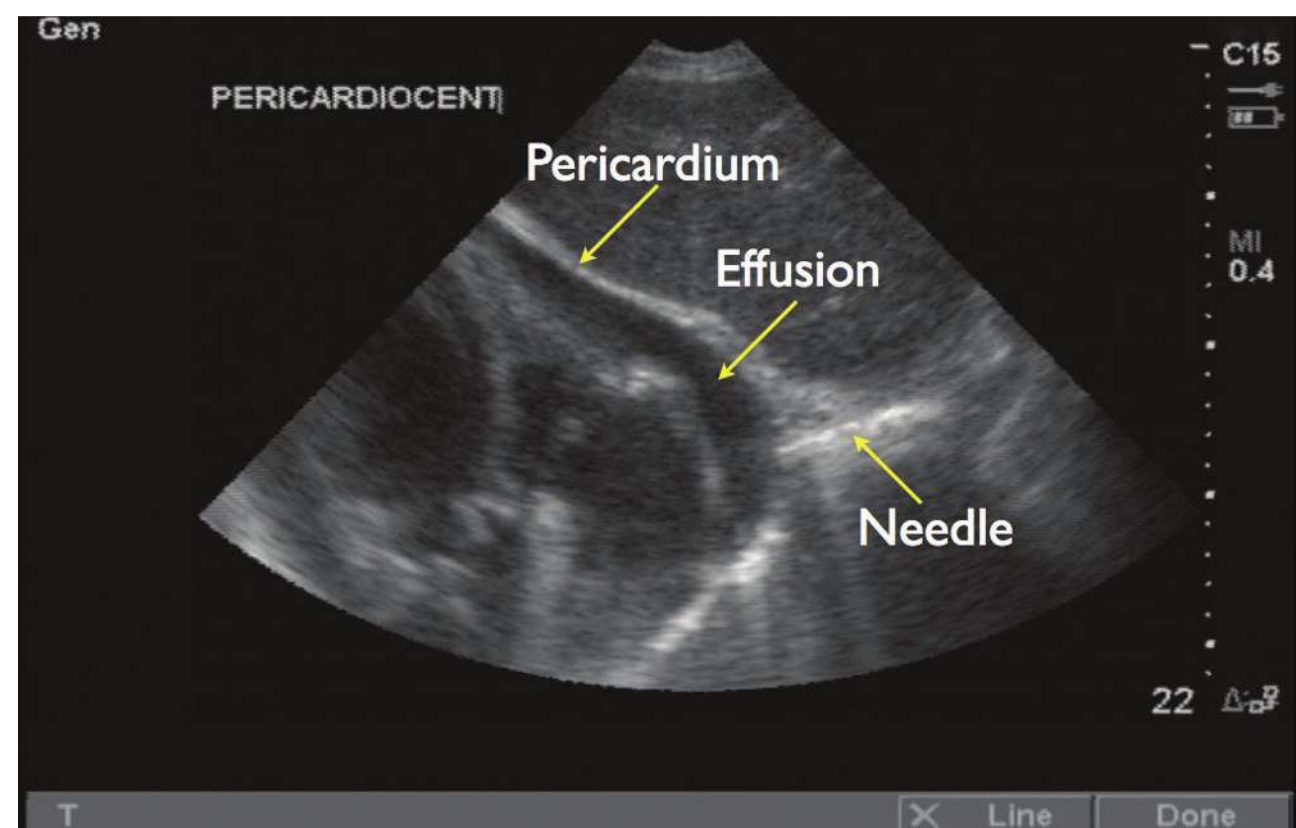


FIGURE 54-19 Pericardiocentesis with needle entering largest pocket of fluid.

placement of the tip by the presence of bubbles in the pericardial space, identified with ultrasound.⁶⁹

When employing a subxiphoid approach, either static or dynamic sonographic guidance can be used. For the static technique, the probe is positioned in the subxiphoid region. The effusion should be visualized with the largest pocket centered on the screen. The entry point, direction of the needle, and depth necessary to reach the fluid should be noted. After the probe is removed, the needle can be introduced as just described.^{66,70}

THORACENTESIS

Pleural effusion is a relatively common entity among critically ill patients, and thoracentesis is the most common interventional thoracic procedure.⁷¹ The etiology of the collection can be elusive and pathologic examination of a fluid sample is often diagnostic. Potential complications of thoracentesis include pain, pneumothorax, vasovagal reactions, re-expansion pulmonary edema, and inadvertent liver or splenic laceration, as well as infection and hemothorax.^{71,72} Ultrasound can be used not only to detect an effusion but also to guide drainage, which may be necessary to perform emergently if the pleural fluid is causing respiratory distress. Ultrasound is more sensitive than chest radiography for detecting pleural effusions. It has also been shown to increase the success rate of thoracentesis and to decrease the rate of complications,^{71,72} including pneumothorax and lacerations of the liver and spleen.⁷³

To detect a pleural effusion by ultrasound, place the patient in a supine position with the head of the bed at 45 degrees. The low-frequency curved abdominal probe should be placed longitudinally in the mid- or posterior axillary line just inferior to the nipple so that the curved hyperechoic line of the diaphragm above the liver or spleen can be visualized. A pleural effusion will be represented by an anechoic collection of fluid superior to the diaphragm. In addition, when no effusion is present, the abdominal spinal stripe will terminate at the diaphragm; the thoracic spine should not be visualized because the ultrasound waves are refracted by the air-filled lungs. However, when an effusion is present, the fluid collection allows for visualization of the thoracic spine superior to the diaphragm (Figure 54-20). Once an effusion has been detected, a more thorough evaluation of the chest should be performed. The movement of the lung with the respiratory cycle and the location of the diaphragm and abdominal organs should be noted so as to avoid these structures when a thoracentesis is performed.

When performing a thoracentesis in a cooperative awake patient, the patient can be placed in the sitting position at the edge of the bed with his or her arms folded on a tray table. The posterior hemithorax should be scanned with a small footprint phased array or a micro convex probe from the inferior scapular border to the upper lumbar region, and then from the paraspinal region to the posterior axillary line, in order to delineate the extent of the fluid collection and the area of the largest pocket.⁷³ A hyperechoic line, representing

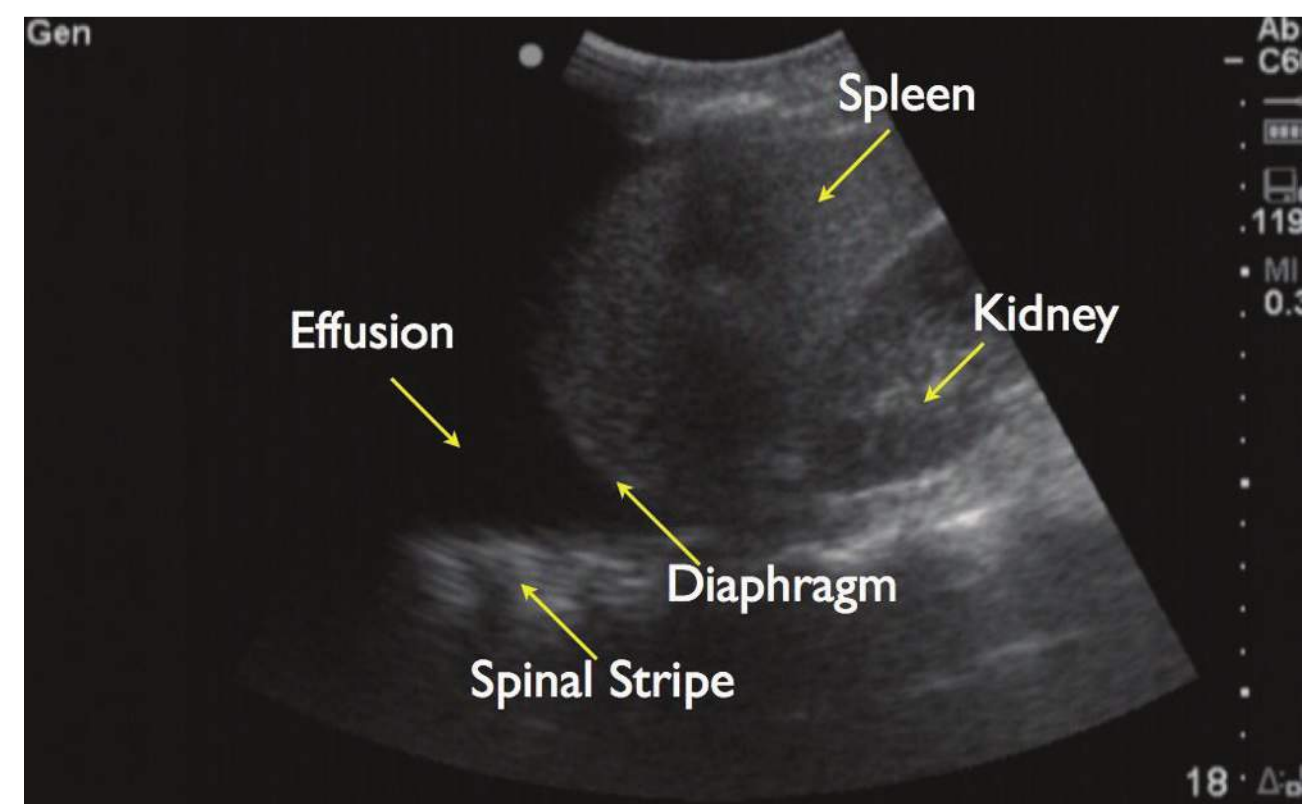


FIGURE 54-20 Pleural effusion with the hyperechoic line representing the spinal stripe extending beyond the diaphragm, indicative of an effusion.

the pleura, should be visible between the ribs. Noting the depth of the pleura will be useful to determine the distance the needle will need to traverse to successfully aspirate fluid.⁷⁴ After the effusion is mapped out, the critical structures of the diaphragm and the lung are located, and the entry point is determined and marked. A static approach is employed, and the procedure proceeds in the normal fashion. Care must be taken to ensure that the needle is placed superior to the diaphragm. The hyperechoic diaphragm should be visualized and the needle should be introduced at least two rib spaces above this structure to ensure that the peritoneal cavity is not violated. The procedure can also be performed dynamically, visualizing the needle as it enters the pleural space. If a thoracostomy tube is to remain in the thoracic cavity, a location in the midaxillary line will be more comfortable for the patient when lying in the supine position.

A sedated or intubated patient requiring a thoracentesis should be placed in the supine position with the arm abducted and the stretcher in the reverse Trendelenburg position. The puncture site will be in the lateral chest in the midaxillary line similar to the location commonly used for chest tube placement. Ultrasound can help to target the largest fluid pocket and to avoid critical structures. If the patient is mechanically ventilated, temporarily decreasing the tidal volume during the procedure may reduce the incidence of pneumothorax. While pneumothorax is a significant complication in the mechanically ventilated patient, the incidence is decreased with use of ultrasound.⁷⁵

PARACENTESIS

Paracentesis is performed in the critically ill patient with ascites for diagnostic or therapeutic reasons, or both. It has been previously demonstrated that physical examination is not an accurate method to assess for the presence of ascites.⁷⁶ Sonographic evaluation of a patient with a markedly distended abdomen that was thought to be due to ascites may reveal little or no free fluid in the abdomen. This discovery can lead to a change in patient management and potentially spare the

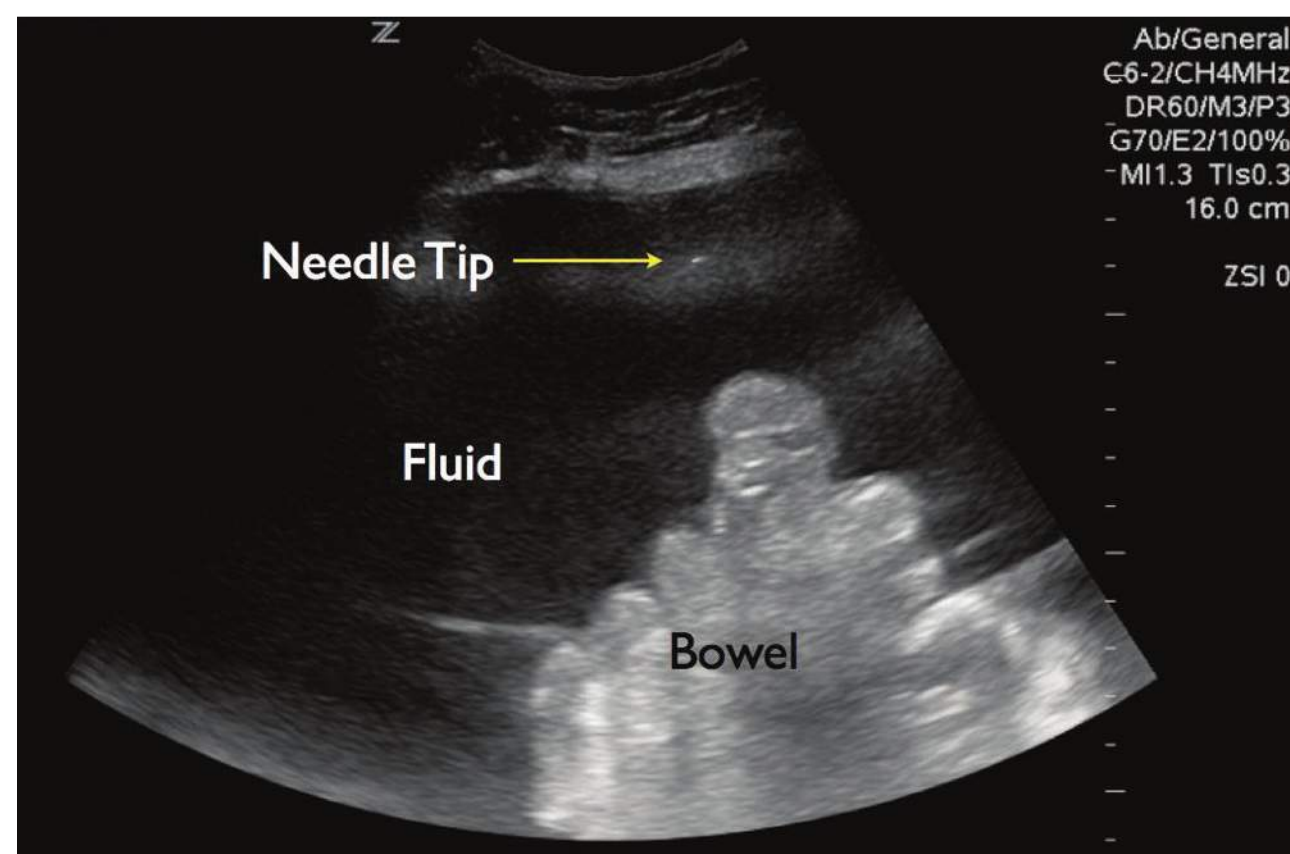


FIGURE 54-21 Paracentesis. Needle tip in abdominal fluid.

patient a paracentesis. If a paracentesis will be performed, US guidance has been shown to confer a much higher success rate when compared with a landmark-based technique (95% vs. 61%).⁷⁷ In addition, large studies have demonstrated a decrease in complication rate, hospital charges, and hospital length of stay in patients who underwent paracentesis with sonographic guidance when compared to those undergoing this procedure using an anatomic landmark technique.^{77,78}

With the patient supine or in a slightly left lateral oblique position and the head of the bed slightly raised, the lower abdomen should be scanned in two orthogonal planes with the low-frequency curved transducer. The left lower quadrant has been traditionally preferred because a gas-filled cecum or an appendectomy scar inhibiting the free flow of fluid may be present in the right lower quadrant. The use of sonographic guidance allows for identification and avoidance of vital intra-abdominal structures, so either lower quadrant may be utilized. The largest fluid collection site should be noted and the entry point marked. A fluid collection tube at least 3 cm in diameter is considered adequate for drainage. Static guidance is most commonly used for this procedure, although one may use dynamic guidance to observe the needle entering the peritoneum (Figure 54-21).

Structures to note and avoid when scanning the abdomen are the inferior epigastric artery in the abdominal wall, the bladder, and the intestines. The thickness of the abdominal wall and the depth of the fluid collection should be noted as well. Also note that a large loop of fluid-filled bowel should not be mistaken for a fluid collection. Fluid-filled bowel has a hyperechoic wall surrounding it and exhibits peristalsis, whereas peritoneal fluid will be located outside the intestinal walls.

ENDOTRACHEAL INTUBATION

Unrecognized esophageal intubation is relatively infrequent, although in those rare occurrences, morbidity and mortality are significantly increased.⁷⁹ There are multiple methods employed at the bedside to confirm endotracheal intubation including direct visualization of the tube passing between the

vocal cords, chest rise after intubation, auscultation over both lungs, and end-tidal carbon dioxide monitoring. However, any single method is not entirely reliable. While capnography is often considered the criterion standard for confirmation of endotracheal intubation, this method can be inaccurate in a number of clinical scenarios including cardiac arrest, massive pulmonary embolism, and diminished cardiac output states.⁸⁰

Ultrasound has recently been shown to be useful as a bedside adjunct for confirming endotracheal intubation. Using the high-frequency linear array transducer, ultrasonography should be performed dynamically during the intubation procedure. Just prior to intubation, the vocal cords can be visualized as a triangular structure. The probe is held transversely over the cricothyroid membrane. As the endotracheal tube is passed, a brief “snow storm” should be seen.^{79,81} Normally, the esophagus will appear as a collapsed soft-tissue structure adjacent to the trachea. However, in the setting of an esophageal intubation, the esophagus may be noted to be distended by the endotracheal tube, and the esophagus will demonstrate a “ring down” reverberation artifact due to the air-filled endotracheal tube. The esophagus will have a similar appearance to the normal trachea. A recent meta-analysis demonstrated ultrasonography to have a pooled sensitivity and specificity of 93% and 97%, respectively, for the detection of esophageal intubation.⁸² In addition, confirmation of bilateral lung sliding should be performed by placing the linear transducer longitudinally over both hemithoraces anteriorly in order to check for pleural sliding. The presence of bilateral sliding provides confirmation of an endotracheal intubation and helps to differentiate a right mainstem bronchus intubation from a tracheal intubation. The absence of lung sliding may indicate an esophageal intubation, right mainstem intubation, or other lung pathology (Figures 54-22 and 54-23).^{79,81–85}

CHEST TUBE PLACEMENT

Subcutaneous placement of a chest tube is a known complication of tube thoracostomy. While chest radiography is routinely used, differentiating tubes that appear intrathoracic in the anteroposterior radiographic view but are actually extrathoracic can be challenging. Computed tomography (CT) of the chest is more sensitive and specific in identifying correct tube placement. However, this imaging modality requires a patient to be moved to the radiology suite, which may be inadvisable in an unstable patient. CT is also costly, time-consuming, and exposes the patient to significant ionizing radiation. Ultrasonography can be utilized for verifying intrathoracic versus extrathoracic tube thoracostomy placement.⁸⁶

Using a linear array high-frequency transducer placed in a transverse orientation relative to the chest tube, the tube will appear as a hyperechoic arc with a “ring down” reverberation artifact. Starting at the site where the tube pierced the skin, the tube is followed, and the disappearance of the arc indicates that the tube entered the pleural space.⁸⁶ Visualization of the arc superior to the thoracostomy site for the length of the tube indicates that the tube is in the subcutaneous tissue.⁸⁷

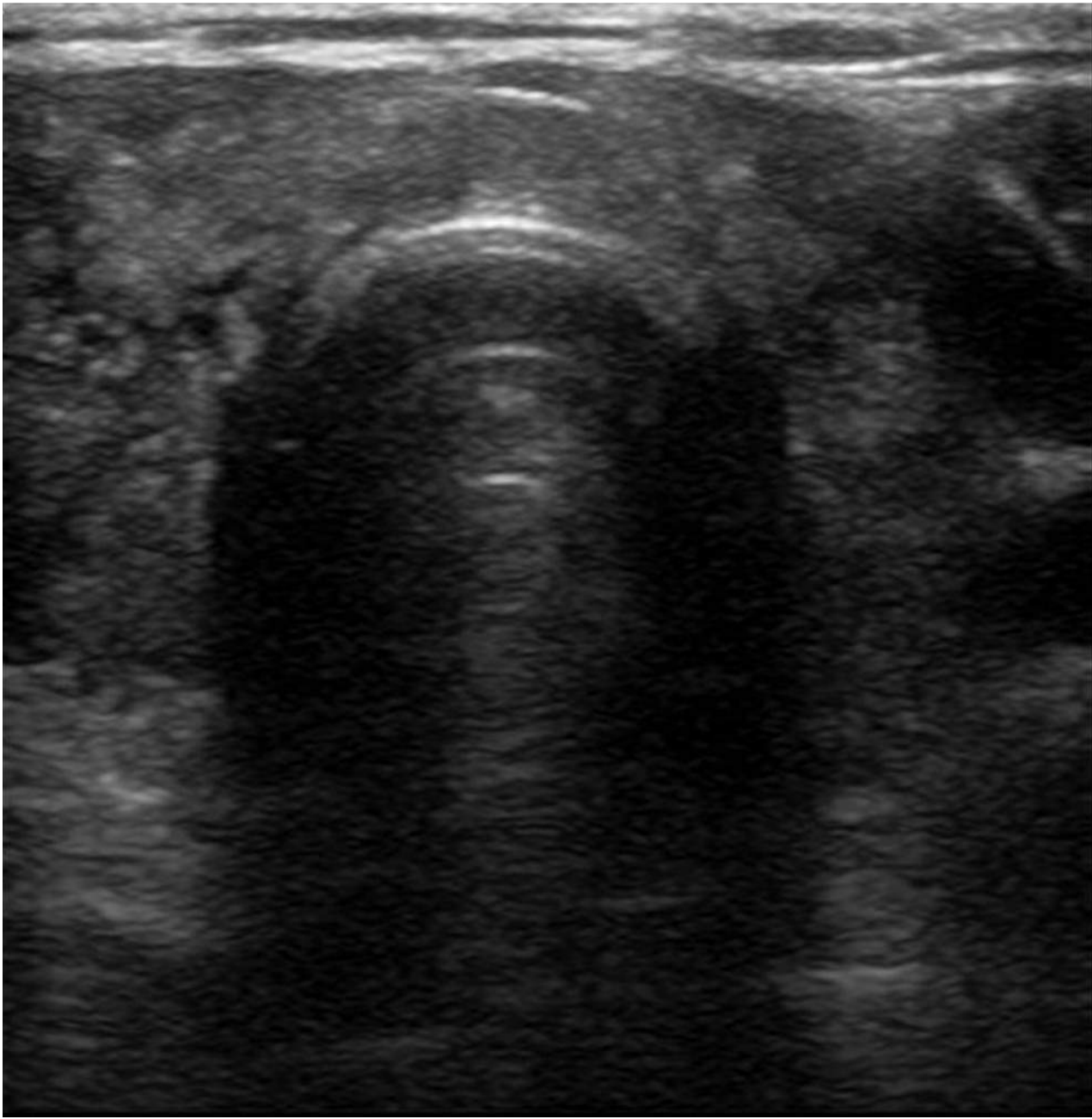


FIGURE 54-22 Trachea before intubation with ring-down artifact.



FIGURE 54-23 Trachea with endotracheal tube in place demonstrating posterior shadowing from the tube and loss of ring-down artifact.

LUMBAR PUNCTURE

Lumbar puncture is a commonly performed procedure used to aid in the diagnosis of meningitis, subarachnoid hemorrhage, and other neurologic emergencies, and in the treatment of idiopathic intracranial hypertension. Traditionally, the procedure relies on identification of bony landmarks. However, these landmarks may be difficult to palpate or identify due to body habitus, contractions, or inability to properly position the patient. Furthermore, using Tuffier's line between the iliac crests to identify safe lumbar interspaces may be inaccurate.⁸⁸ Ultrasound guidance has been shown to decrease the rate of failed lumbar punctures, the number of attempts, the rate of traumatic procedures, and the number of needle redirections.^{89,90} Sonographic guidance may be particularly helpful when performing lumbar puncture in patients with an elevated body mass index.⁹¹

To perform the procedure, the patient is ideally placed in the sitting position with the hips flexed. The feet can be supported by a stepstool or chair, and the patient should be leaning forward.^{92,93} This position is not possible in every clinical scenario, so the lateral decubitus position may also be employed. The linear high-frequency probe is preferred. In an obese patient, a low-frequency probe may be used if deeper sonographic penetration is necessary to visualize bony structures. The probe is placed in a transverse orientation. The hyperechoic spinous process and the associated posterior acoustic shadowing confirm that the midline is being visualized. The transducer is then rotated 90 degrees to convert to a longitudinal orientation. Beginning at the top of the gluteal fold, the hyperechoic bony sacrum is visualized. Moving superiorly, the first break in the hyperechoic line is the L5–S1 disc space. The L5 spinous process appears as a hyperechoic convex line with posterior acoustic shadowing. Moving the transducer superiorly, the three lower spinous processes and the intervening disc spaces can be mapped out. The probe can be moved laterally to find the lateral margins of the spinous processes as they disappear from view. The probe can also be turned 90 degrees to better appreciate the lateral margins of the spinous processes (Figure 54-24).^{94,95} With indelible ink, the central line of the spine and each spinous process can be drawn on the skin. These marks, rather than palpation of bony landmarks, can be used to determine the optimal needle insertion site when performing a lumbar puncture.

CONCLUSION

There is a growing body of literature demonstrating the value of ultrasonography in the care of the critically ill patient. Ultrasound is widely available, portable, repeatable, relatively inexpensive, pain-free, and safe. This imaging modality has utility not only for diagnostic purposes, but also for guidance of invasive procedures, often allowing these procedures to be performed more efficiently, with a higher success rate, and with fewer complications when compared to landmark-based techniques.



FIGURE 54-24 Static longitudinal view of L3–L4 interspinous space.

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Ultrasound Assessment for Volume Status

Ashika Jain • Deborah Shipley Kane

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INTRODUCTION

Assessing volume status in critically ill and injured patients is of paramount importance to the provider and patient. However, volume status can be very difficult to assess and is often dynamic. Studies such as that by Rivers et al. have shown that early aggressive fluid resuscitation directly impacts sepsis outcomes.¹ Yet studies such as the SOAP trials noted that positive fluid balance was among the strongest prognostic factors for mortality.² There are various methods by which to assess fluid status. Bedside ultrasound assessment of volume status has become an important tool for the clinician because it is non-invasive, not harmful, and, most importantly, repeatable for reassessment. Pulmonary artery catheters for pulmonary wedge pressure have been shown to provide no added benefit to patient care, with the added burden of increased cost.^{3–6} The use of central venous pressure (CVP) as a single marker has come under much scrutiny since Marik et al. described a poor relationship between CVP and blood volume in a systematic review in 2008 and again in 2012.^{7,8} This chapter will review these methods for using bedside ultrasound for evaluation including inferior vena cava (IVC) ultrasound, cardiac ultrasound, superior vena cava (SVC) ultrasound, and pleural ultrasound.

To read more about CVP, pulmonary artery occlusion pressure (PAOP), and other methods of hemodynamic monitoring, please refer to Chapter 15 (hemodynamic and perfusion monitoring).

HEMODYNAMIC ASSESSMENT

Hypoperfusion and volume overload are associated with increased morbidity and mortality in critically ill patients. Volume status is integral to resuscitation efforts. Indications

for assessment include cases of volume depletion (evaluating for presence and extent of hemorrhagic shock or dehydration), volume overload (as in cases of decompensated cardiac failure), and serial monitoring for response to fluid therapy in cases of sepsis or to direct resuscitation (fluids versus adding inotropic medications). Traditional methods for intravascular volume status assessment are invasive and associated significant complications. Ultrasound is a painless, nonirradiating, noninvasive imaging tool that can be used repeatedly at the bedside and avoid complications associated with invasive monitoring, including arterial puncture, venous thrombus, and infection.

A quick and safe bedside maneuver to establish fluid responsiveness is the passive leg raise (PLR). PLR has been widely used as an endogenous fluid bolus. With the patient in a stretcher, the head is reclined to supine with the legs raised 45 degrees, passively. This results in a 150–500 cc bolus, depending on the patient's volume reserve. Duus et al. suggest that it is more reliable than fluid challenge.⁹ In various studies, PLR has been shown to increase PAOP, end diastolic left ventricular dimensions, and CVP. Since this is a reversible process once the legs are brought back to the supine position, opportunity for untoward harm from a bolus is minimized.¹⁰ This information can be used to direct resuscitation efforts in the critically ill patient.

ULTRASOUND FOR FLUID ASSESSMENT

Probe and Equipment Selection

The general tools needed to perform these applications will be a bedside ultrasound machine, an ultrasound probe, ultrasound gel, and personal protective equipment. Each



FIGURE 55-1 Transducers. Phased array, most often used for cardiac windows; curved, for deep structures; and linear, most often used for superficial structures and venous access.

application may use different probes and tools, and each will be covered individually. The two main ultrasound probes that will be used are the phased array probe and the linear array probe (Figure 55-1). The phased array probe is a low-frequency probe that may be used in many cardiac and abdominal applications. The linear array probe is a high-frequency probe often used for vascular or superficial applications. Probe selection may also depend on patient characteristics (e.g., obesity), probe availability, preset calculations needed, and time available.

Setup

Place the patient in the supine position. The degree of elevation of the head of the bed has not been shown to make a significant difference in measurements. A low-frequency probe, such as a phased array or curvilinear probe, should be selected. The examiner may want to stand to the patient's right side, if the examiner is right-hand dominant.

Inferior Vena Cava Ultrasound

The measurement of the IVC as an assessment of volume status has been described in humans as early as 1979.¹¹ Much literature and discussion has been directed to this noninvasive tool since that time, establishing its usefulness at the bedside. This section will focus on the basics of IVC measurement, as well as the most current literature.

IVC MEASUREMENT

Multiple locations and orientations have been described for the measurement of the IVC, including subxiphoid long, subxiphoid short-axis, right upper quadrant/mid-axillary line, and transpyloric long- and short-axis (Figures 55-2 and 55-3). Although no single view has been validated, most experts and literature recommend the subxiphoid long-axis



FIGURE 55-2 Subxiphoid view of the inferior vena cava (IVC) with hepatic vein entering just below the diaphragm.

view. To obtain this view, start with the standard subxiphoid four-chamber cardiac view and identify the right atrium and right ventricle. Then rotate the probe posteriorly toward the spine, with the probe indicator to the patient's right, to identify and follow the IVC in short axis. The IVC is to the right of patient's midline, thin-walled, and has respiratory flow variation on color Doppler; it should be distinguished from the thick-walled aorta. To visualize in long axis, rotate the probe indicator 90 degrees to the patient's head. In this view, one should see the length of the IVC, including its entrance into the right atrium above the diaphragm and the confluence of the hepatic veins that drain into the IVC (Figures 55-2 and 55-3). The IVC diameter should be evaluated approximately 2 cm inferior to the hepatic veins or 2–3 cm from the junction of the right atrium.^{12–14}

Once the proper location is identified, the practitioner should evaluate for respiratory variation in the size of the

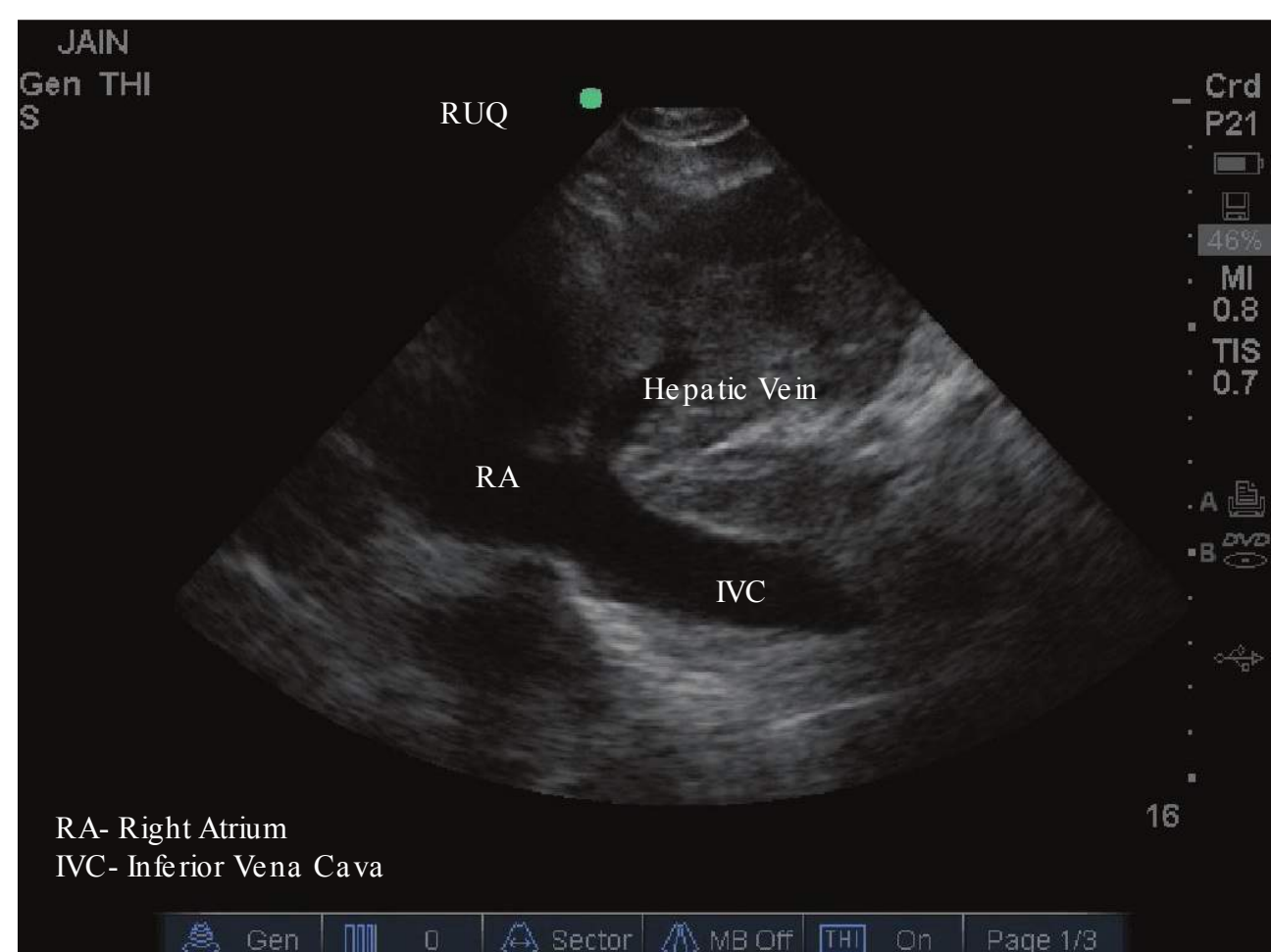


FIGURE 55-3 Right upper quadrant view of the inferior vena cava (IVC) with hepatic vein entering just below the diaphragm. Making note of the hepatic vein ensures that the measured vessel is the IVC, rather than the aorta.

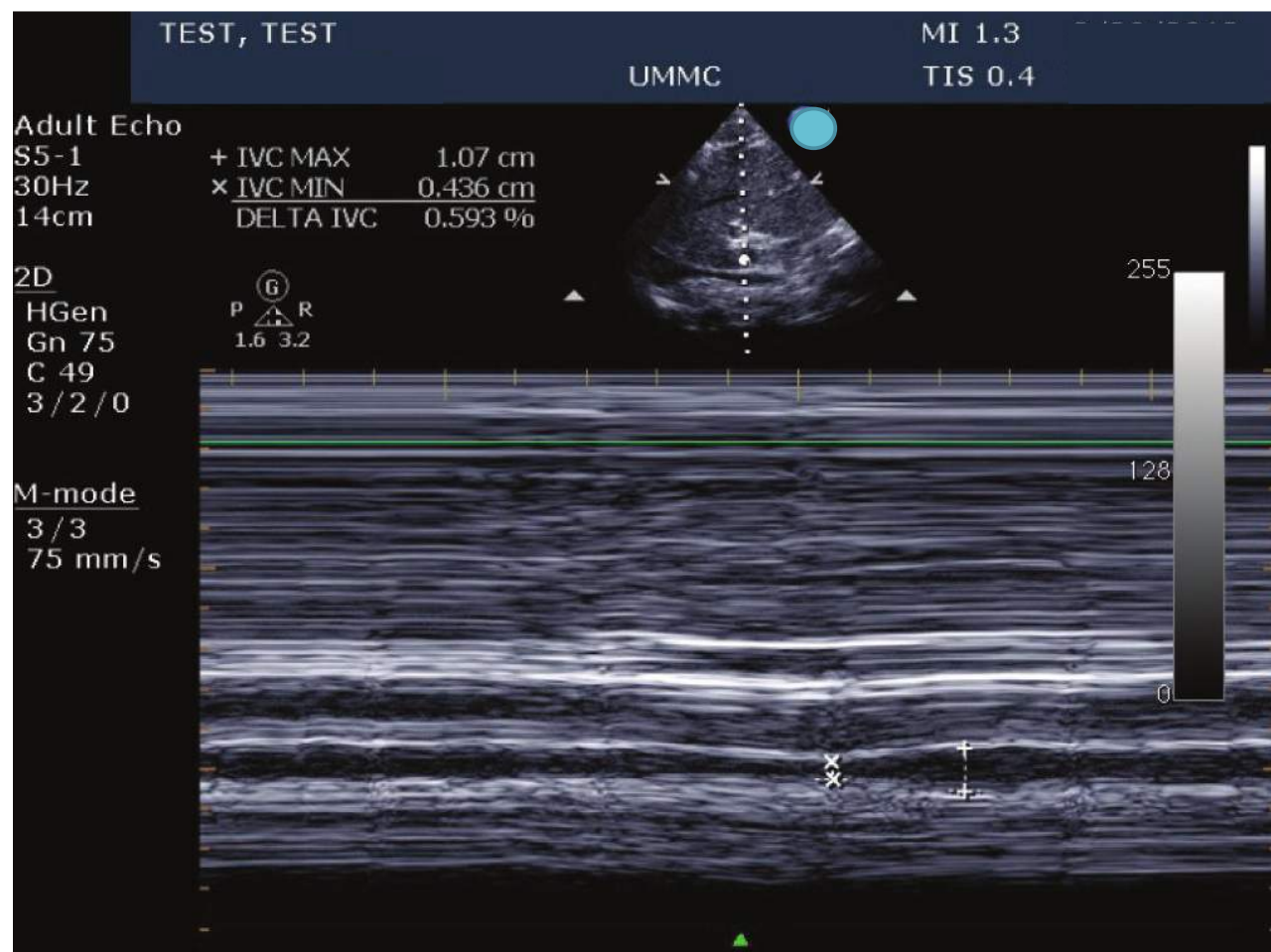


FIGURE 55-4 M-mode view of IVC diameter change in the from the subxiphoid window. The M-mode spike is placed 2–3 cm below the diaphragm to avoid pulsatile changes from the heart. The minimum and maximum diameters are measured. The IVC collapsibility index, caval index, and distensibility index can be calculated from these measurements.

IVC. In a spontaneously breathing patient, the IVC should show a normal pattern of collapse during inspiration. This is due to the negative intrathoracic pressure generated with inspiration. In a mechanically ventilated patient, the IVC will show collapse with expiration. The IVC diameter can be measured in B-mode in inspiration and expiration. In addition, the IVC can be visualized and measured in M-mode (Figure 55-4). To measure in M-mode, obtain the long axis of the IVC. Place the M-mode cursor over the area to be measured (see above) and press the M-mode button again. A tracing will be generated in which one can see the change in size of the IVC, and it can be easily measured once the figure is frozen.

TYPICAL MEASUREMENTS AND MEANINGS

Based on previous literature, many sources cite different measurements of the IVC and the correlation with CVP and right atrial pressure. We will review the most common measurements of the IVC.

IVC maximum: This is the maximum size of the IVC. Diameter measured from wall to wall in long or short axis

IVC minimum: The smallest diameter of the IVC. This can be measured in long or short axis

These are the most commonly used measurements for the inferior vena cava. Early studies have used absolute cutoff numbers and correlated them with CVP measurements.

IVC collapsibility index (IVC-CI): Expressed as the difference between the maximum diameter and the minimum diameter, divided by the maximum of the two values. $((D_{\max} - D_{\min}) / D_{\max}) \times 100$. Usually used in

nonventilated, spontaneously breathing patients. Studies suggest cutoffs of $> 40\%$ for empty and $< 15\%$ for full.^{15,16}

Caval index: $IVC \text{ expiratory diameter} - IVC \text{ inspiratory diameter} / IVC \text{ expiratory diameter} \times 100 = \text{caval index } (\%)$.

In general, numbers closest to 100% are indicative of almost complete collapse (and therefore volume depletion), whereas a number close to 0% suggest minimal collapse (i.e., likely volume overload). Kircher et al. first defined the caval index in 1990, showing that a cutoff of $> 50\%$ correlated to right atrial pressure of < 10 mm Hg.¹⁷ In 2010, Nagdev et al. went on to look at the correlation of caval index and CVP. Of 73 patients enrolled, 32% had a CVP of < 8 mm Hg. A caval index of $> 50\%$ had a strong association with a CVP of < 8 , with a sensitivity of 91% and specificity of 94%.¹⁸

Distensibility index (dIVC): Measured in mechanically ventilated patients, where the IVC diameter (D) at end-expiration is (D_{\min}) and at end-inspiration is (D_{\max}). The distensibility index of the IVC (dIVC) is calculated as the ratio of $D_{\max} - D_{\min} / D_{\min}$ and expressed as a percentage. A cutoff of 18% has a 90% sensitivity and specificity to predict volume responders versus nonresponders.¹⁹

SPONTANEOUS VERSUS MECHANICALLY VENTILATED

Although there is controversy about using IVC measurements in the spontaneously breathing patient versus in the mechanically ventilated, there are considerations for each. Use of IVC for fluid status was described in spontaneously breathing patients on hemodialysis.^{20,21} It has also been used in trauma patients to guide resuscitation in spontaneously breathing patients who show evidence of shock.^{22,23} In mechanically ventilated patients, there is a reversal of IVC measurements with respiration. The IVC diameter will be maximal with inspiration due to positive pressure into the thoracic cavity and minimal with expiration. Most of the current evidence utilized IVCCI without adjustments for positive pressure. Sensitivity and specificity range from 71–90% and 90–100%, respectively.^{19,24} The IVC becomes larger and less compliant in most intubated patients.²⁵ One technique describes placing the patient on temporary, high tidal volume (10 mL/kg) ventilation and evaluating IVC diameter changes. A patient would be considered fluid responsive if the IVC changes by 15–18%.

Another limitation of the using ultrasound for IVC measurements is interrater reliability, ranging from location of measurement to M- versus B-mode and oblique imaging planes. If a measurement is done in an oblique plane, a false measurement is obtained, thereby leading to inaccurate calculations. Additional variability is related to movement of the vessel relative to the transducer during the respiratory cycle, which results in unintended comparison of different points of the IVC at end expiration and inspiration, possibly

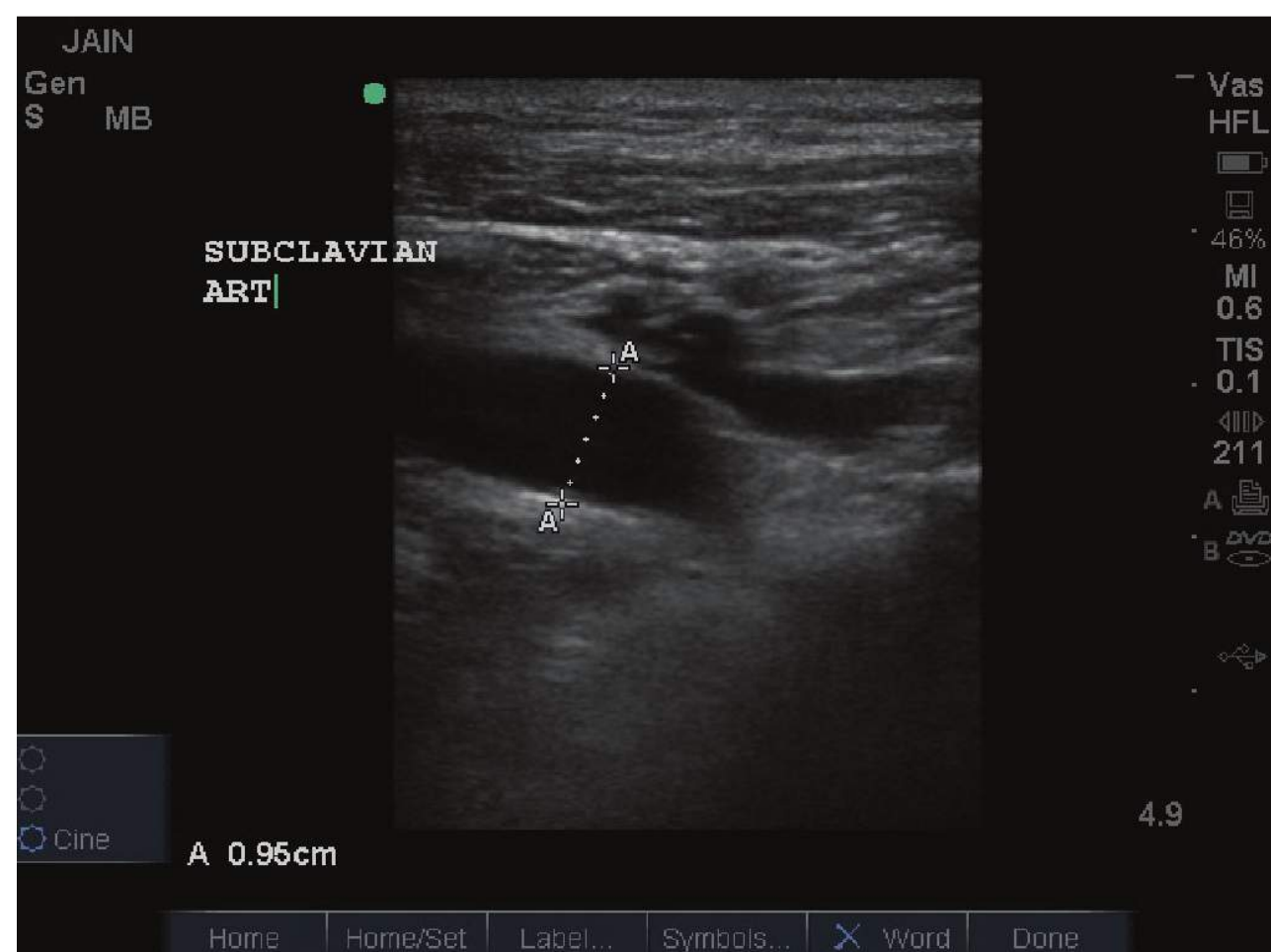


FIGURE 55-5 B-mode image of the subclavian vein maximum diameter.

introducing error related to variations in normal anatomy.²⁶ Last, interoperator variation among experienced sonographers (fellowship trained) was 0.60, with 95% confidence interval (CI) of 0.36 to 0.76 agreement for visually estimated IVC collapse.²⁷

In general, repeated examinations of the IVC with fluid loading may be more helpful than a static one-time measurement because volume responsiveness of the patient has been correlated with progressive filling of the IVC over time.²⁵

SUBCLAVIAN VEIN MEASUREMENT

There are many factors that can make IVC measurements technically difficult, including body habitus, bowel gas, and postoperative dressings. An alternative is subclavian vein measurements for subclavian vein collapsibility (SCV-CI). Kent et al. describe a technique using the high-frequency linear array probe in the sagittal plane at the delta-pectoral triangle. Similar to IVC measurements, the SCV-CI was derived using M-mode for the variation of vein diameters. The calculation for collapsibility is similar to that used for IVC: the difference between the maximum (D_{max}) and minimum (D_{min}) diameters of the target vein divided by the maximum SCV-CI = $[(D_{max} - D_{min})/D_{max}] \times 100$ (Figures 55-5 and 55-6).²⁸

CAROTID ARTERY MEASUREMENT

An additional measurement to evaluate for fluid status as well as fluid responsiveness is the common carotid artery velocity time integral (VTI). There are various studies depicting its reliable application in the clinical setting.²⁹⁻³² Similar to the benefit of using subclavian vein measurements, the carotid artery is a superficial vessel, making it relatively easy to access. Blehar and Stolz describe using a high-frequency liner probe to obtain antero-posterior measurements of the common carotid artery diameter in systole within approximately 0.5 cm of the common carotid bulb in the long axis. The Doppler gate is placed in the middle of the artery with a

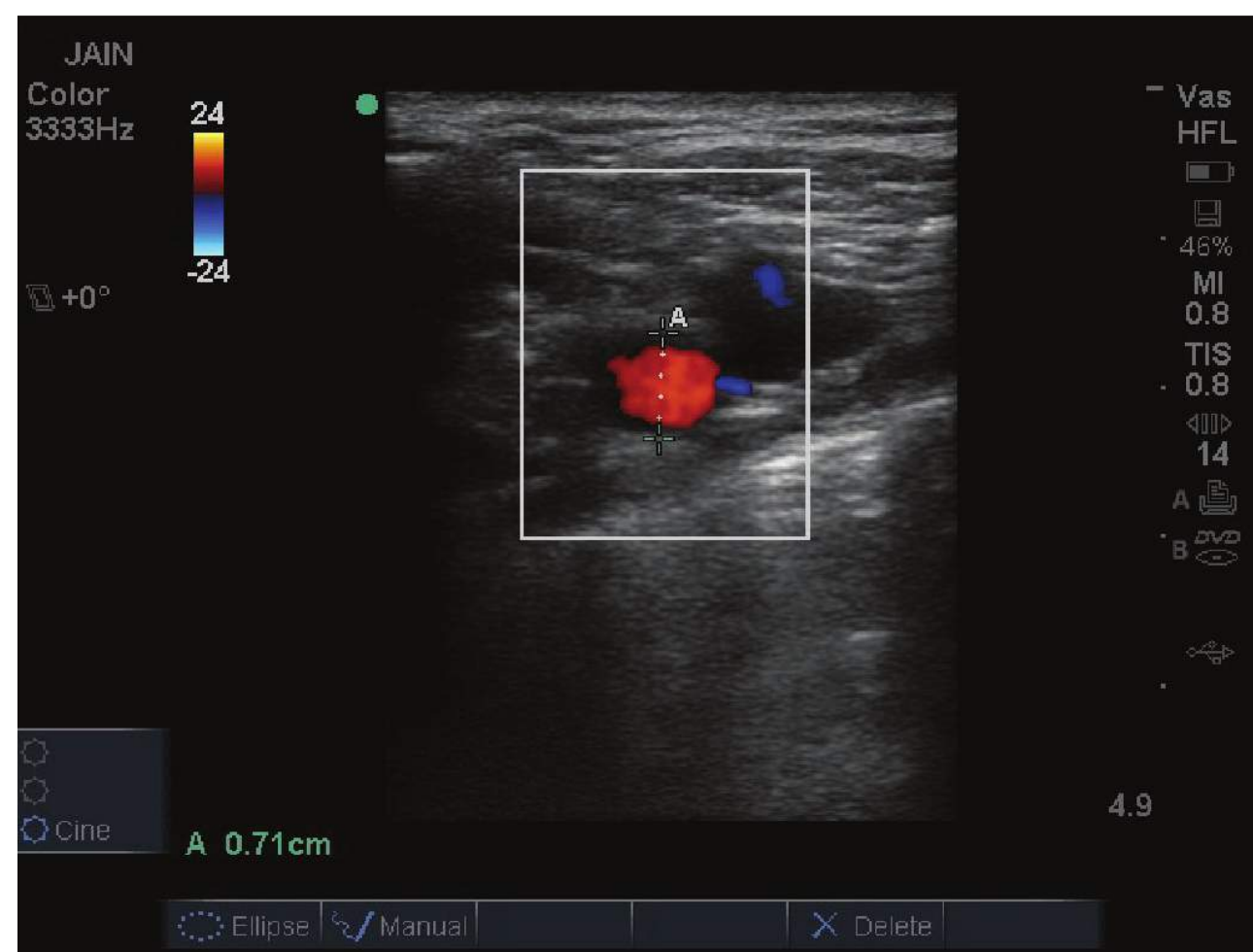


FIGURE 55-6 B-mode image with color Doppler to confirm artery versus vein for subclavian minimum diameter in the same patient in Figure 55-5.

45- to 60-degree angle of insonation, the VTI is then determined through digitalized Doppler spectral envelopes with the sample obtained at the location at which the diameter was taken.^{30,31} Mackenzie et al. describe a similar technique in patients pre and post whole blood donation. In this study, they found corrected carotid artery flow time was able to depict with passive leg raise acute blood loss as well as measure restored volume to predonation levels.³² Carotid artery flow time cannot be performed in patients with significant valvular dysfunction, aortic or carotid artery disease, or dysrhythmias (Figures 55-7 and 55-8).

ALTERNATIVE VEINS

Given the limitations of IVC imaging, internal jugular vein (IJV) and femoral veins are also described as alternative locations for fluid responsiveness. There is some discordance of

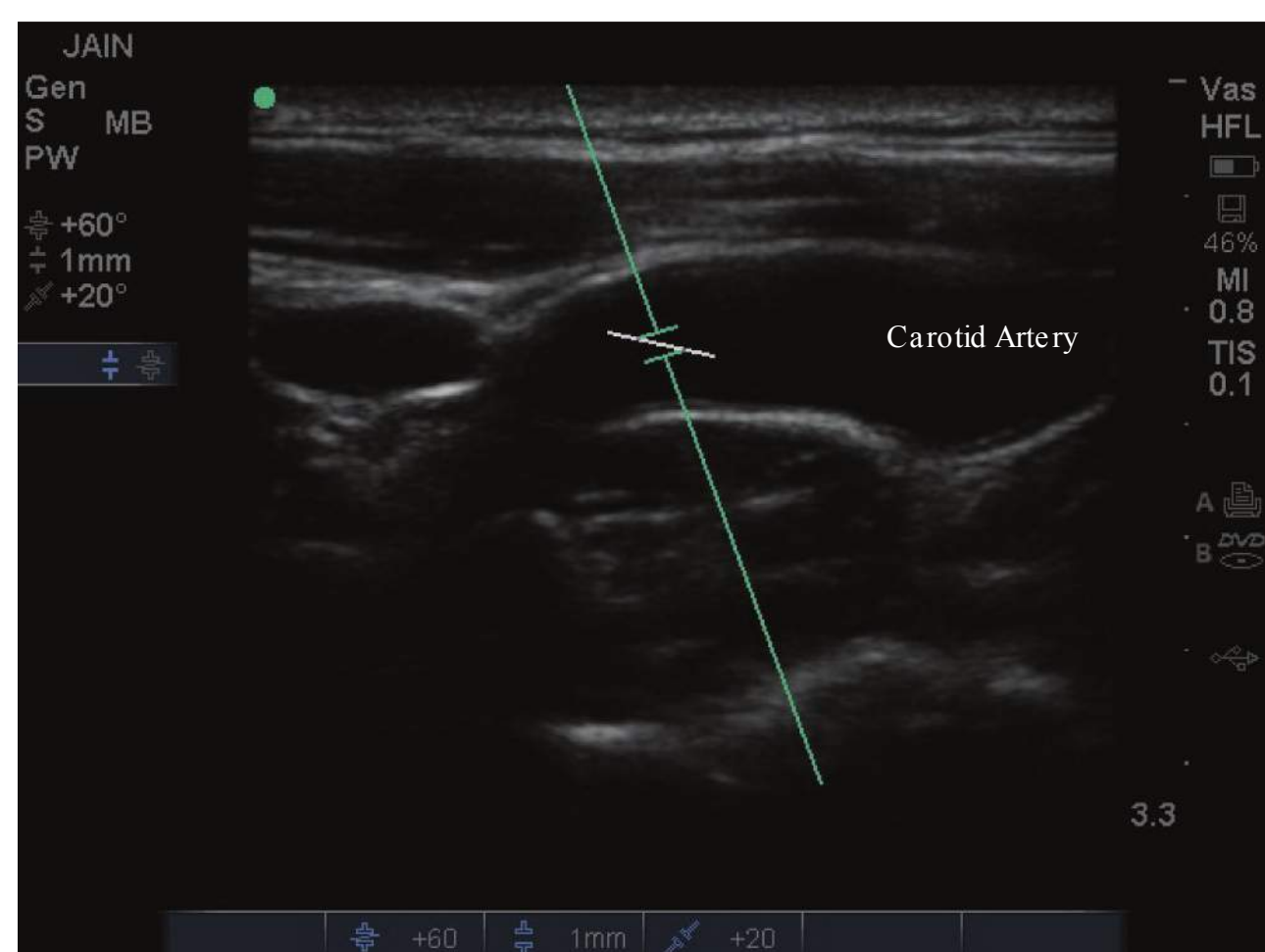


FIGURE 55-7 Doppler gate in the common carotid artery just below the bifurcation.

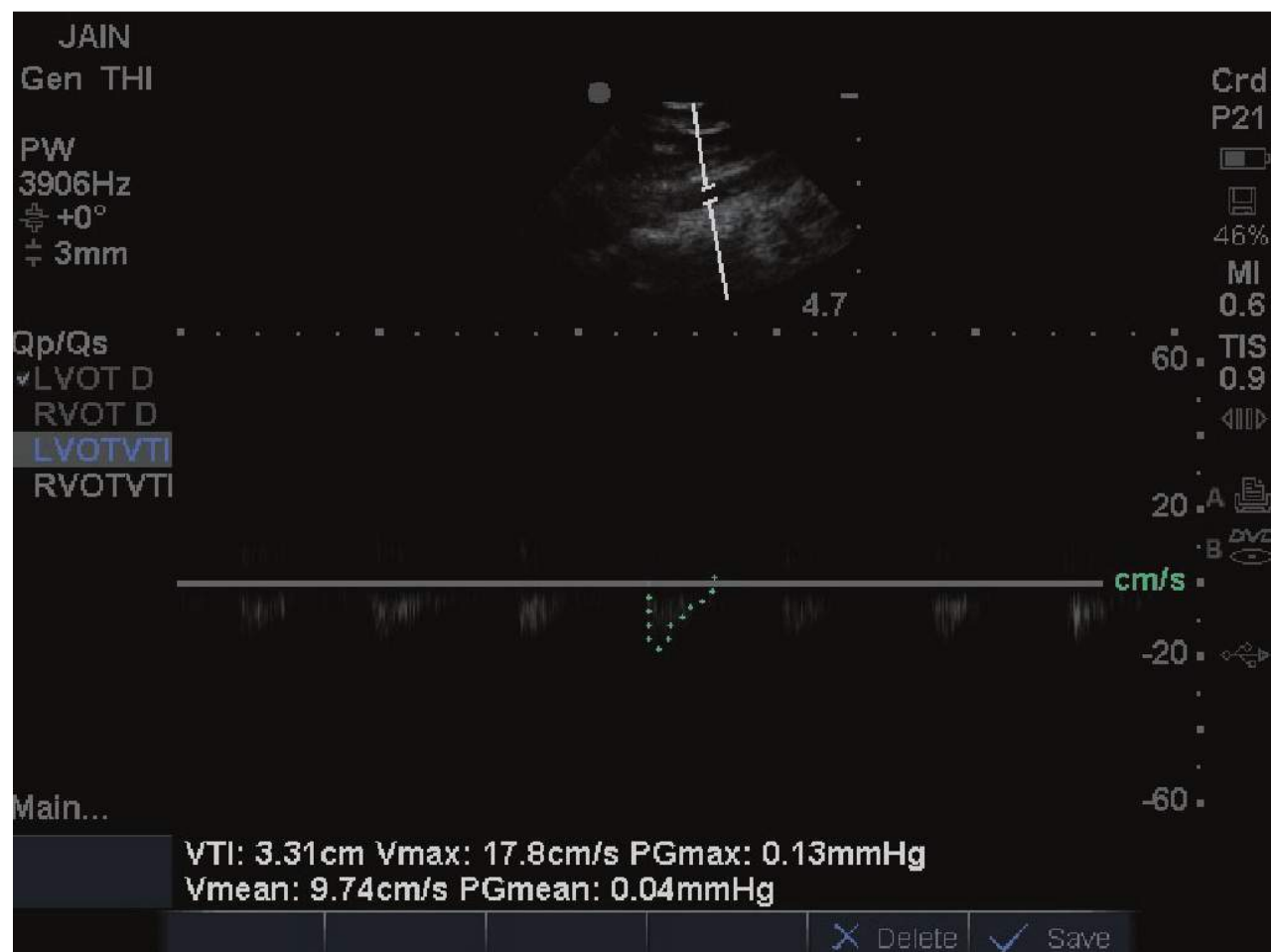


FIGURE 55-8 Common carotid artery velocity time integral (VTI).

evidence on the use of the IJV. IJV distensibility is defined as the ratio of the difference between the IJV maximal antero-posterior diameter during inspiration and minimum during expiration to the minimum expiratory diameter $\times 100$. Guarracino et al. describe an 18% IJV distensibility to have a sensitivity of 80% and 85% specificity for fluid responsiveness.³³ Kent et al. looked at the IJV collapsibility index (IJV-CI) as well as the femoral vein collapsibility index (FV-CI) as compared to IVC-CI. In both cases, correlation was weak, with overestimation of IJV-CI and underestimation of FV-CI.³⁴

CARDIAC EVALUATION

Understanding volume status in a critically ill patient should take the whole patient into consideration. CVP and IVC, as well as the plethora of adjunct veins, all describe preload; however, they do not correlate with afterload interpretation. The cardiac index (CI) is considered the reference standard parameter for targeting organ perfusion and oxygen delivery in shock.³⁵

Bedside ultrasound can be used for CI, left ventricular outflow tract (LVOT) diameter, VTI, and stroke volume variation (SVV). To calculate CI, the LVOT diameter and VTI are required. The LVOT diameter is the diameter of the aortic outflow tract in the parasternal long view of the heart just distal to the aortic valve. VTI is an estimation of the distance that a column of blood travels in 1 systolic stroke, or *stroke distance*, in the apical five-chamber view with a pulsed-wave Doppler cursor near the aortic valve annulus. Using cardiac software to calculate the VTI, the Doppler signal is traced.³⁶⁻³⁸

$$CI = SV \times \text{heart rate (HR)}$$

$$SV = LVOT \text{ area} \times LVOT \text{ VTI or } \pi \times (LVOT \text{ diameter}/2)^2 \times VTI$$

Limitations to the calculations are arrhythmias such as atrial fibrillation; however, in this case, using an average of

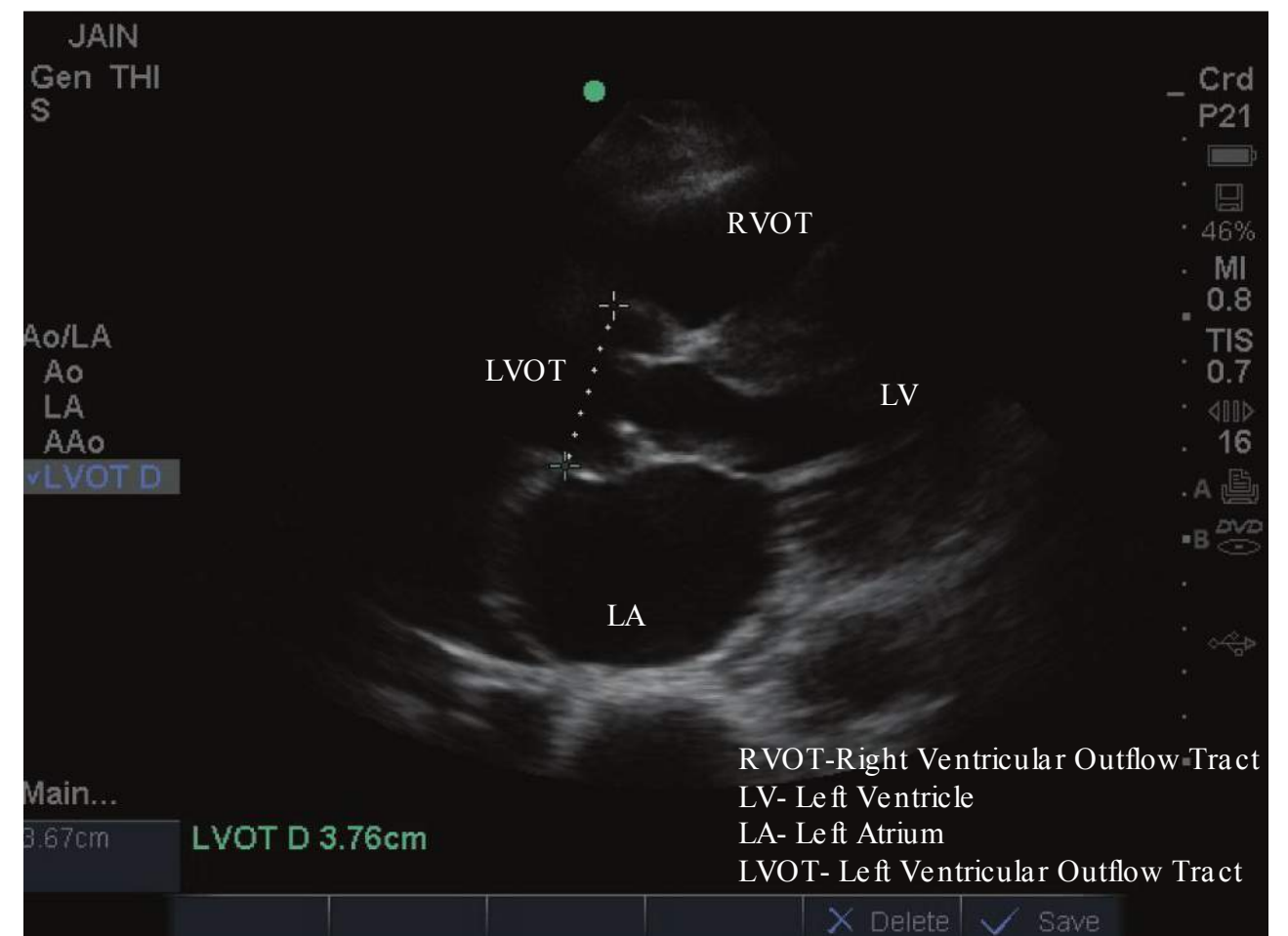


FIGURE 55-9 B-mode echocardiography of parasternal long window for left ventricular outflow tract diameter (LVOT D). This measurement can be used to calculate cardiac output.

several beats has been described as an alternative. Additionally, an inaccurate measurement of the LVOT can introduce significant error in output values since the radius is squared. Regardless, in the same patient, using the same LVOT diameter will give useful information about changes in cardiac output (Figures 55-9 to 55-11).

SVV has been described as a useful tool to assess fluid responsiveness; however, traditionally, this was described using thermodilution via PAOP.^{39,40} In the apical four-chamber view of the heart, respiratory variation of the SV velocity in the Doppler mode can be calculated as $SVV = ([SVV_{\max} - SVV_{\min}] / SVV_{\max}) \times 100\%$. In a systematic review and meta-analysis, Zhang et al. found an diagnostic odds ratio of 18.4 for SVV to predict fluid responsiveness.⁴¹ Normal SVV in ventilated patients is 10–13%; $> 13\%$ SVV is associated with a fluid responsive state.⁴² Limitations of SVV

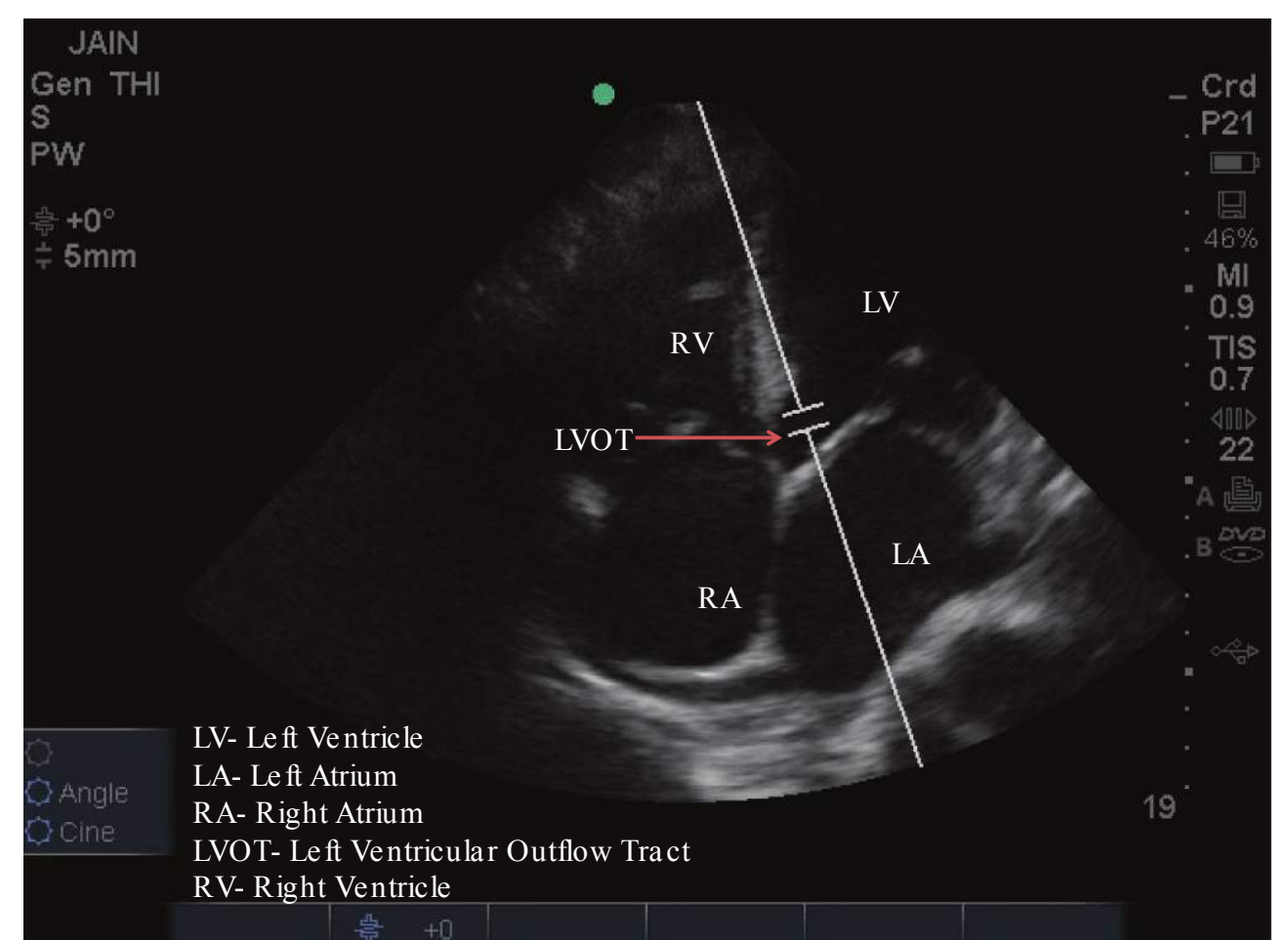


FIGURE 55-10 Apical five-window with Doppler gate in the left ventricular outflow tract (LVOT) for LVOT velocity time integral (VTI).

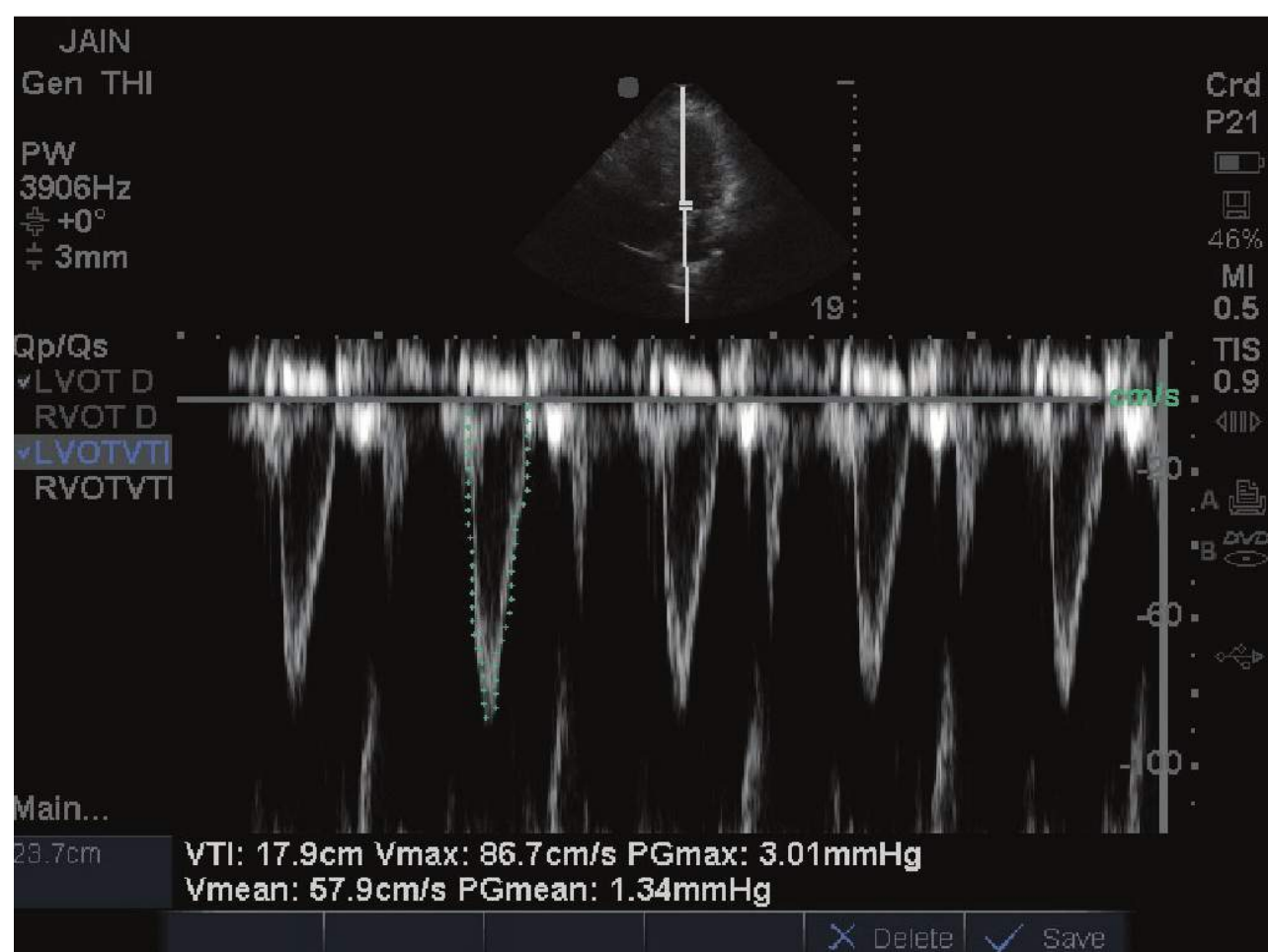


FIGURE 55-11 Left ventricular outflow tract (LVOT) velocity time integral (VTI) to calculate cardiac output.

include arrhythmias and patients ventilated with high PEEP because this may increase SCC and vascular tone, which may increase SVV (Figure 55-12).

FLUID TOLERANCE

Excessive fluid resuscitation with an accumulating positive fluid balance is associated with worse clinical outcomes.^{2,43} The idea of fluid tolerance describes a patient's ability to tolerate fluid resuscitation. Intubating a patient with iatrogenic pulmonary edema may not always be an option, nor does it come without consequences (e.g., increased length of stay, increased morbidity and mortality).

Fluid tolerance should be frequently assessed during resuscitation when trying to avoid intubation or aid with interventions, such as inotropes.

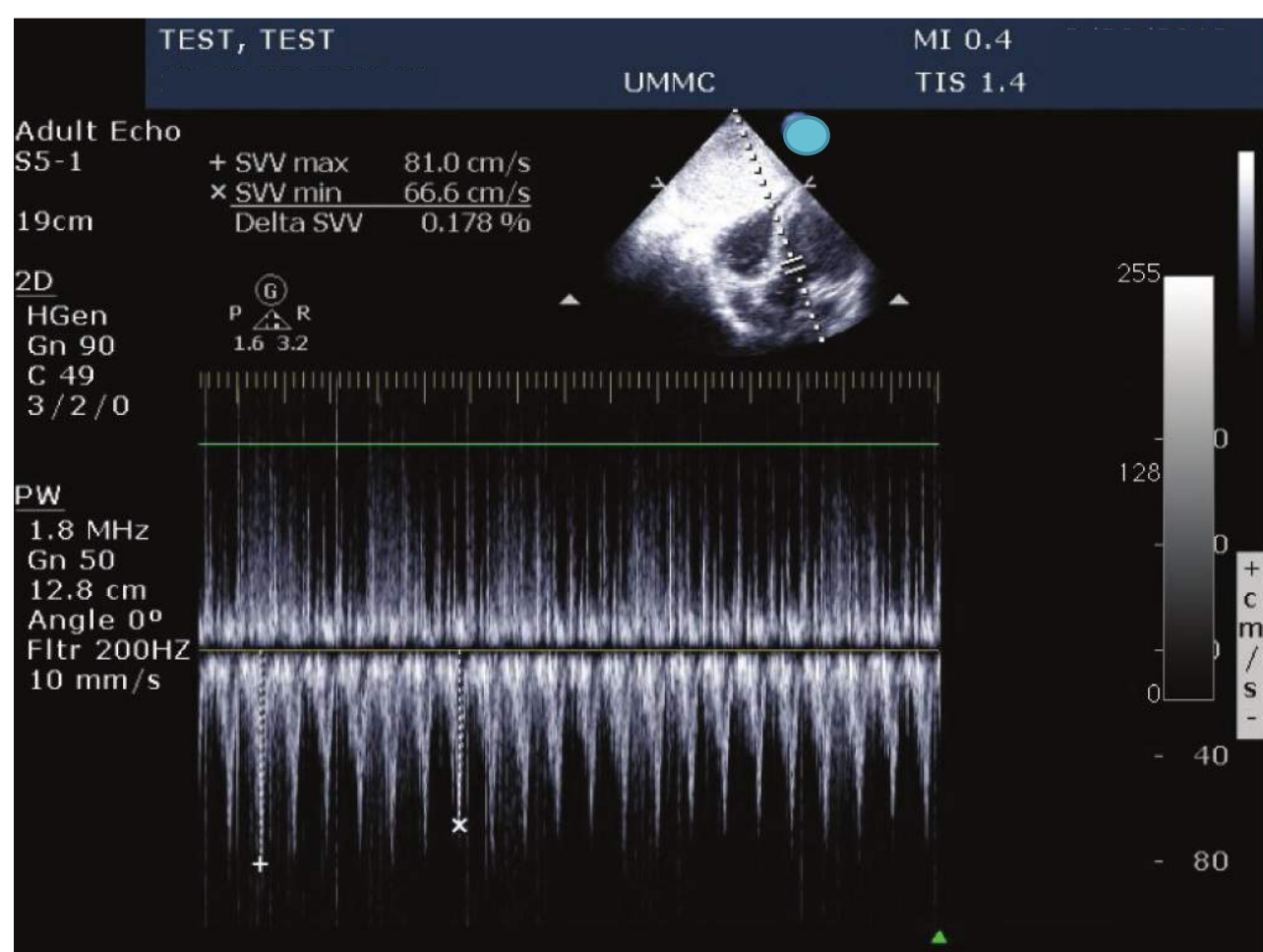


FIGURE 55-12 Doppler gate in the left ventricular outflow tract for stroke volume variation. The minimum and maximum velocity are used to calculate the delta.

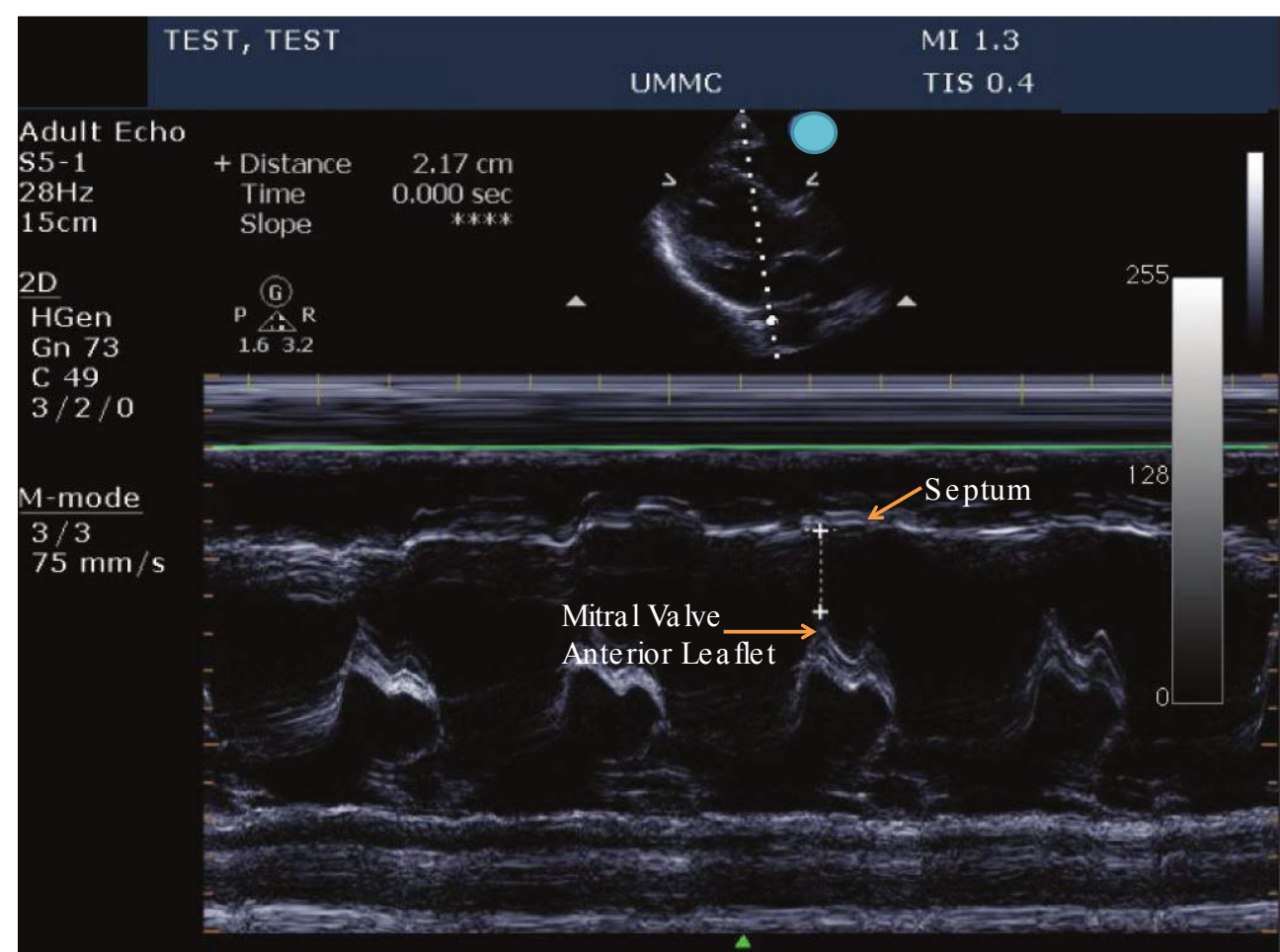


FIGURE 55-13 Parasternal long window with M-mode spike at the tip of the mitral valve anterior leaflet. The minimum distance from the septum to the anterior leaflet, or end-point septal separation (EPSS) is used to calculate ejection fraction (EF).

Ejection fraction (EF) can be visualized and followed to consider tolerance. While most cardiologist calculate EF by visual estimation, end-point septal separation (EPSS) can be used by the novice echocardiographer. In the parasternal long view, with the M-mode cursor over the distal tip of the anterior mitral valve leaflet, the minimal distance is measured in millimeters. Using the calculation $75.5 - 2.5(\text{EPSS})$, the EF can be calculated.^{44,45} This calculation is a useful tool until the sonographer becomes better acquainted with visual approximation of EF (Figure 55-13).

PULMONARY ULTRASOUND

Although it is imperative to resuscitate patients in shock, the known consequence of pulmonary edema occurs. Performing a bedside pulmonary ultrasound can help to avoid

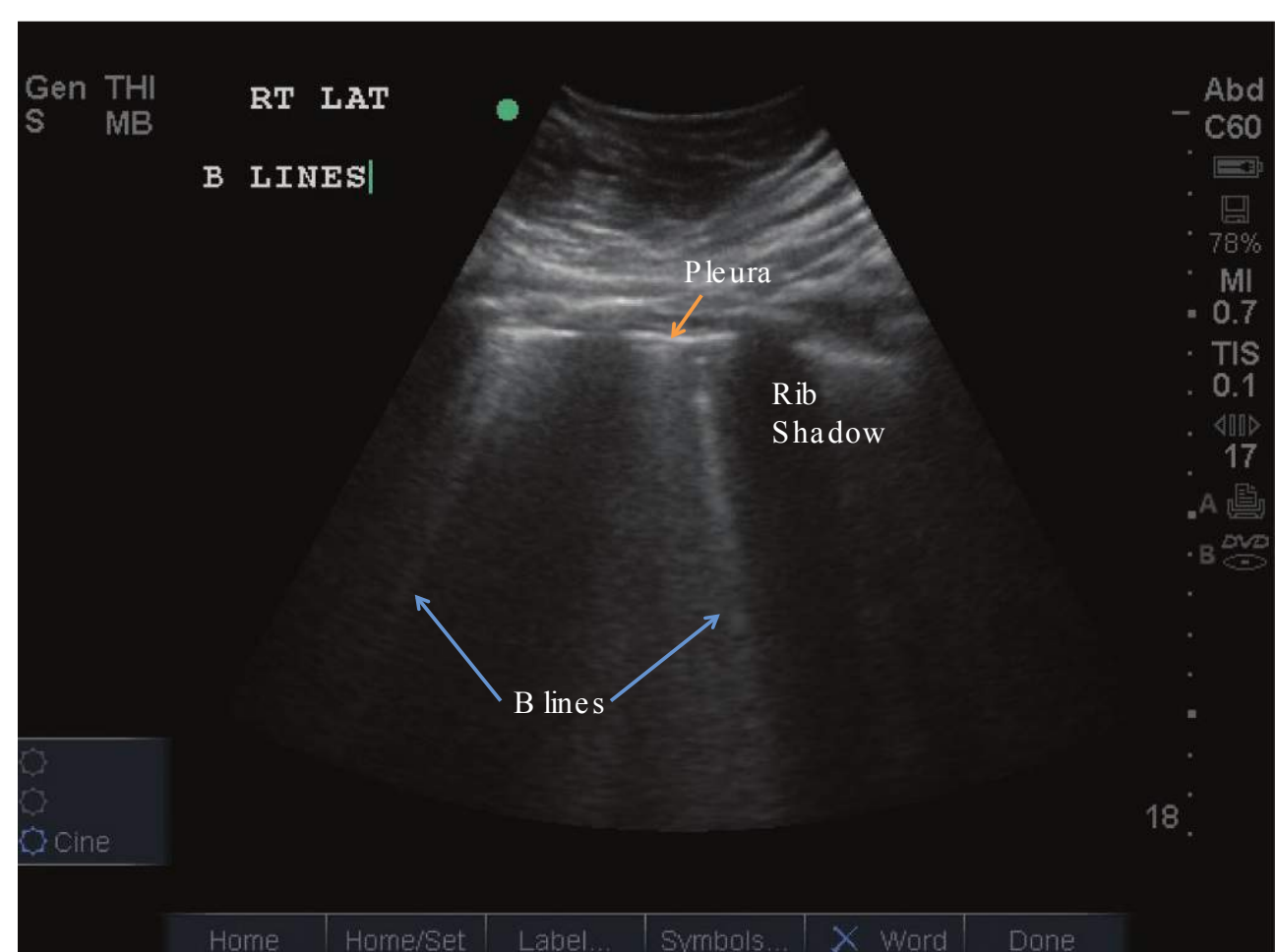


FIGURE 55-14 B-mode of lung window with B-lines. (Used with permission from Michael Secko.)

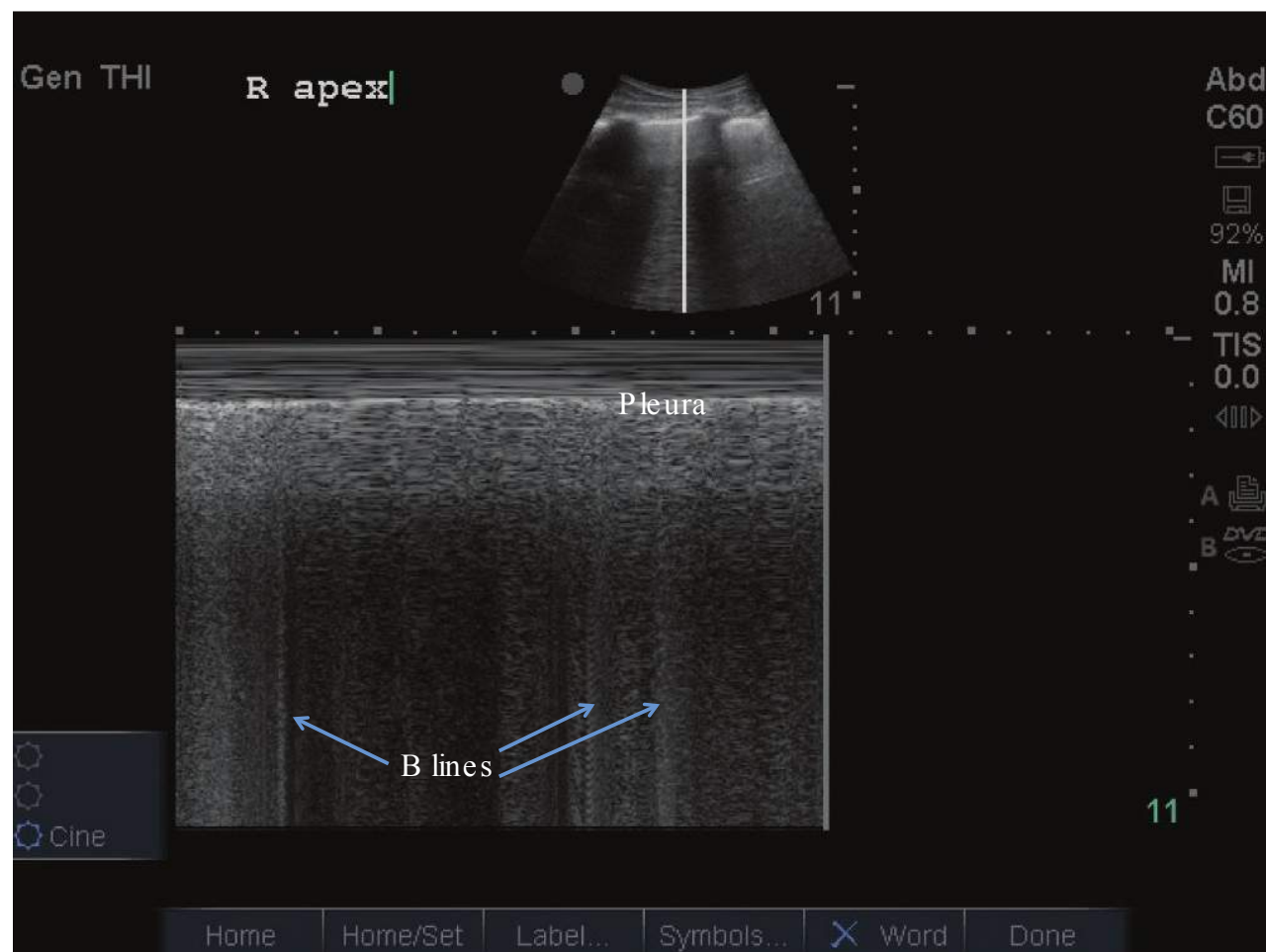


FIGURE 55-15 M-mode of lung window with B-lines. Excessive B-lines is concerning for pulmonary edema. (Used with permission from Michael Secko.)

pulmonary edema. Using a high-frequency linear probe, vertical narrow-based lines arising from the pleural line to the edge of the ultrasound screen can be seen. Sometimes called *comet tails*, this artifact represents the air–fluid interface.⁴⁶ Sonographic B-lines are related to radiographic Kerley B-lines and lung water score on chest X-ray and to extravascular lung water measured invasively by the thermodilution method.^{47,48} Excessive presence of B-lines suggests pulmonary edema. This exam should be done through a systematic, thorough lung ultrasound, looking at a minimum of four windows in each thoracic cavity to ensure accurate diagnosis (Figures 55-14 and 55-15).

USABILITY

Although there is evidence that suggests that ultrasound is a user-dependent modality,²⁷ there is a substantial amount of evidence that exemplifies its use at the bedside with good accuracy and reproducibility. Additionally, bedside sonography can be repeated after an intervention or if patient status changes. Time to evaluation and determination of fluid status is significantly shorter for ultrasound versus more invasive techniques. Bedside ultrasound should be considered in any acutely ill patient, not only to determine the cause of hypotension, but also to guide therapies and resuscitation.

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Ultrasound of the Lung

Diego Casali • Ashika Jain • Christopher Bryczkowski

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INTRODUCTION

Ultrasound was first used to detect a pneumothorax in a horse in 1986, and then described in humans shortly afterward.¹ Lung ultrasonography was pioneered by Dr. Daniel A. Lichtenstein, a French intensivist, in 1993.² In a series of innovative articles, he defined the scope, application, and terminology of lung ultrasonography in current use.³

The need for lung ultrasonography was born from the inherent limitations of the chest radiograph, which has been the standard initial diagnostic imaging test for the past several decades. As a static imaging modality, chest radiographic findings are often delayed compared to a patient's clinical picture (sometimes as long as 24 hours). Also, it is often non-diagnostic when performed on the supine patient, as it often shows nonspecific patterns. Furthermore, it is time- and labor-intensive.

In contrast, ultrasonography of the lung can be rapidly performed at the bedside, can be repeated serially to gauge treatment without exposing the patient to unnecessary radiation, and is cost-effective with many rapid goal-directed applications.

Lung ultrasonography has been shown to be superior to supine portable chest radiographs and similar in yield to chest computed tomography (CT) for the detection of a normal aeration pattern, pneumothorax, pleural effusion, interstitial syndrome, and alveolar syndrome.⁴

BASICS

A 3.5- to 5-MHz curvilinear transducer is often preferred when performing most ultrasonography of the lung, such as evaluating for interstitial disease and pleural effusions. However, a higher-frequency 5- to 10-MHz linear transducer can be helpful for focusing on superficial structures such as the pleural line, as in the evaluation for a pneumothorax.

In the intensive care unit, the patient is typically positioned supine at 45 degrees, with the upper extremities abducted, or in lateral decubitus if undergoing a complete examination. The transducer orientation marker is placed on the left of the ultrasound screen. The probe is held in a longitudinal position, with the indicator facing cephalad, and oriented such that rib shadows lay at either edge of the screen. The transducer is moved freely over the thorax following sequential scan lines, named stages. Stage 1 is defined by the anterior chest wall; Stage 2 includes the lateral wall, from anterior to posterior axillary line; Stage 3 involves the external part of the posterior wall; and Stage 4 adds the internal part of the posterior wall and the apex.³

Ribs are calcified and project an anechoic shadow, as sound waves cannot penetrate through bone. The only exception to this finding is found at the costochondral joints, where ribs become cartilaginous and allow sound to penetrate through the rib.

Because of the opposition of the parietal and visceral pleura, the pleural line typically appears as a single, bright

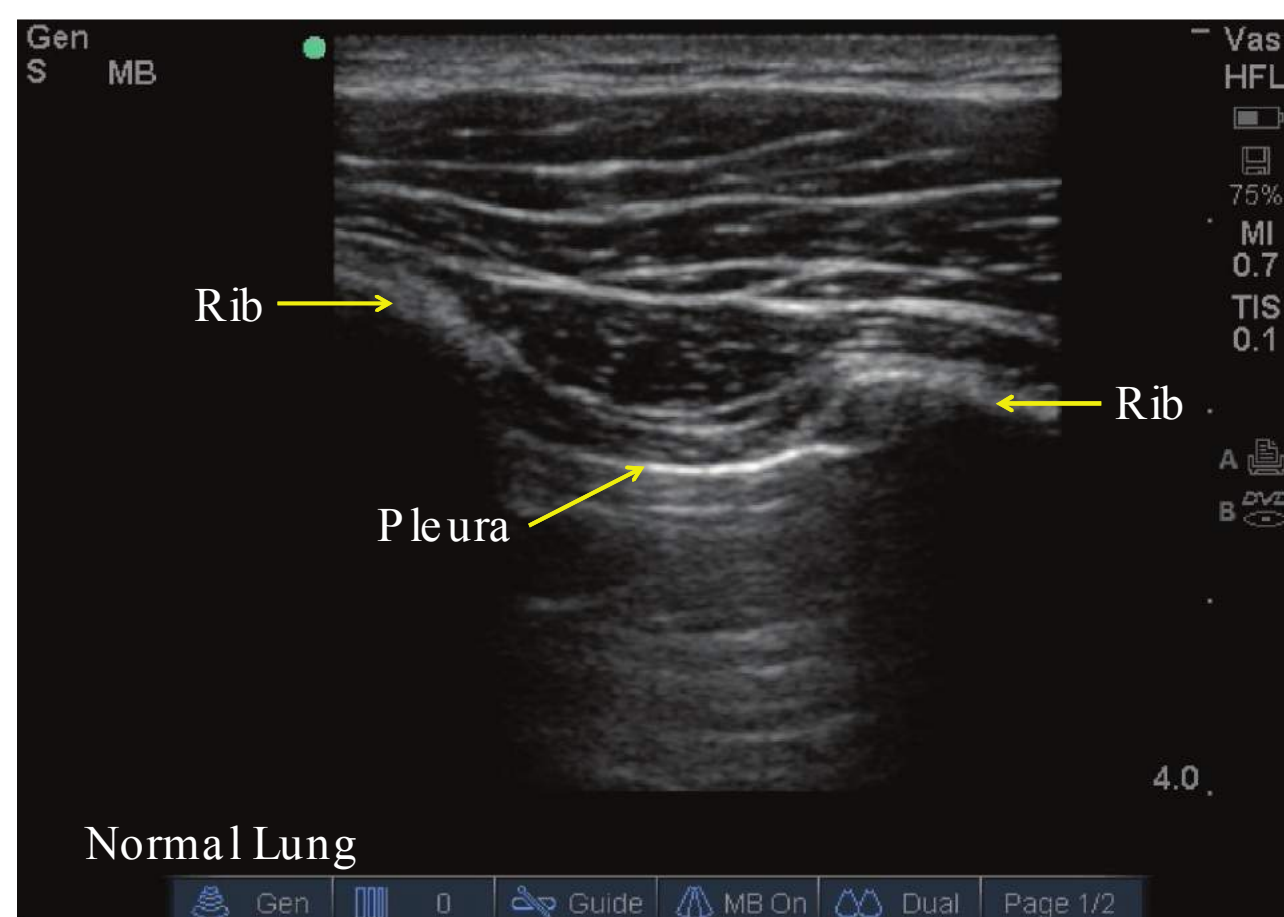


FIGURE 56-1 Normal lung. Used with permission from Ashika Jain.

white line comprised between rib shadows (Figure 56-1). However, the parietal pleura can be separated from the visceral pleura by a large or anterior effusion, which appears as an anechoic stripe.

Lung sliding indicates the inspiratory descent and the expiratory ascent of the visceral pleural against the parietal pleura. It appears as a shimmering of the pleural line that is synchronous with the respiratory cycle and most obvious at the lung base and attenuated at the apex. This is often described as “ants marching.”

Much of lung ultrasonography is dependent on the presence or absence of imaging artifacts as first described by Dr. Lichtenstein. Due to the complex image smoothing algorithms necessary for modern echocardiography, newer ultrasound machines may actually yield inferior-quality images by subduing or even eliminating many of these artifacts. If available, the use of a curvilinear transducer in a “lung” machine setting or the bypass of all imaging filters should allow optimal imaging characteristics for performing lung ultrasonography with modern equipment.

A-LINES

An A-line is defined as a horizontal reverberation artifact created by the bouncing back and forth of sound waves between the skin surface and the pleural line when sound penetrates through underlying normal, aerated lung (Figure 56-2). The presence of an A-line pattern with lung sliding is compatible with a normal aeration pattern, whereas the presence of an A-line pattern without lung sliding indicates the possibility of a pneumothorax.

B-LINES

B-lines (sometimes called comet tails or lung rockets) are created by the reflection and refraction of sound waves through lung that behaves like a parenchymatous organ due to alveolar fluid or interstitial thickening (from fluid or fibrosis). They appear as vertical, bright white lines that originate from the pleura and extend to the full depth of the screen

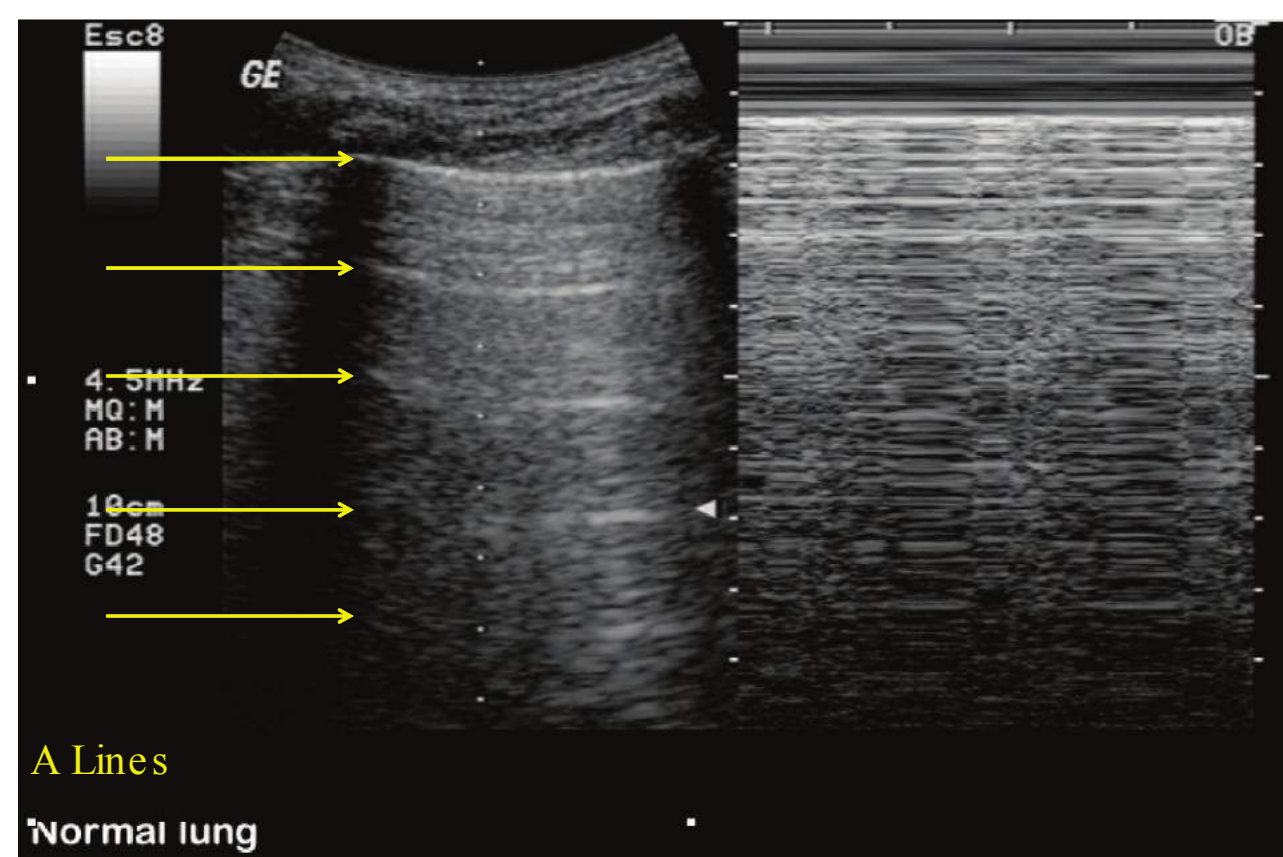


FIGURE 56-2 Parallel hyperechoic A-lines. Used with permission from Ashika Jain.

(Figure 56-3). B-lines strongly correlate with the finding of an alveolar syndrome or interstitial syndrome (ground glass or reticular pattern on chest CT).

B-lines start at the pleural line, efface A-lines at their point of intersection, and reach a depth of at least 18 cm. In addition, they typically move back and forth with respiration. However, they are not necessarily mobile, as in pneumonia where they can be present without lung sliding. Finally, they change their shape based on the amount of interstitial fluid, going from thin, single, vertical lines to coalescing, wedge-shaped lines.³

The amount of B-lines per rib space can range from none (A-lines only up to less than three), to mild (at least three, few in number, intermittently present), moderate (many or partially discrete or partially coalesced B-lines, persistently present), and severe (complete coalescence of B-lines, many in number, persistently present).

Z-LINES

Z-lines also represent artifacts originating from the contact between the parietal pleura and the visceral pleura at the pleural

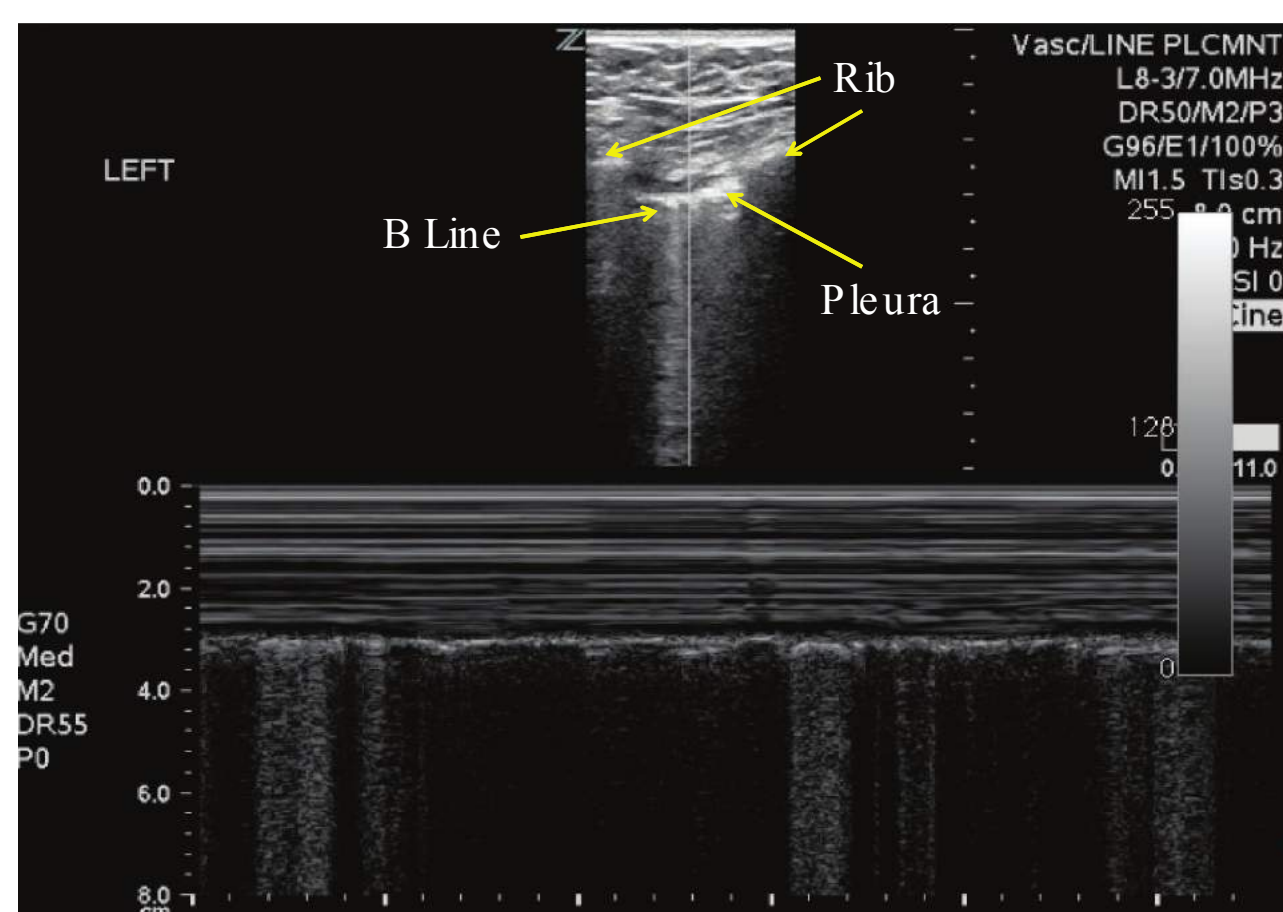


FIGURE 56-3 B-lines originating from the pleura and extending the complete depth of the screen. Used with permission from Ashika Jain.

line but can be distinguished from B-lines because they fade after few centimeters, do not extend to the edge of the screen, and do not overshadow the A-lines.³ This artifact has no specific pathologic meaning and can be present in normal individuals.

PNEUMOTHORAX

The presence of lung sliding of the visceral and parietal pleura rules out pneumothorax in the rib space directly underneath the probe. This should be repeated at multiple areas on the thorax. In the absence of lung sliding, the presence of B-lines, Z-lines, and a lung pulse can also be clues to the absence of a pneumothorax.³ *Lung pulse* is defined as the transmission of cardiac movement through inflated lung to the pleural surface, which is usually more pronounced on the left hemithorax. This is usually overshadowed by normal lung sliding in healthy patients but can be prominent and useful in ruling out pneumothorax in those with a unilateral mainstem bronchial block.

M-mode is often very helpful in identifying the presence or absence of a pneumothorax. Normally, when an M-mode spike is placed over a sliding pleural line, normal lung moves back and forth with the respiratory cycle against the chest wall and appears grainy. This is known as the *seashore sign*. With a pneumothorax, both the chest wall and pleura appear as still, straight lines. The M-mode image is known as the *barcode sign*, or *stratosphere sign* (Figure 56-4).

It is important to remark that the barcode sign signifies absence of lung sliding, which can be present in any process that reduces the entry of air into the lung or fixes the pleura with scarring, as this will reduce or eliminate lung sliding. Examples include apnea, mainstem bronchial intubation, mainstem bronchial occlusion (from a mucous plug, a tumor, a foreign body, a blood clot), pneumonia, severe acute respiratory distress syndrome, and pleural symphysis (inflammatory, neoplastic, cicatricial).

The only pathognomonic finding for pneumothorax is the lung point sign. It is defined as the presence of lung sliding on one half of the ultrasound screen and the absence of lung sliding on the other half when the probe is held at the point where the

visceral pleura reattaches to the chest wall. It may appear as a break in the smooth contour of the pleura or can be visualized in M-mode appearing as alternating seashore and barcode signs. (Figure 56-5A,B). The location of the lung point sign on the chest wall allows an estimation of the size of the pneumothorax.¹²

Because pneumothoraces contain air that will rise above the more dense lung parenchyma, the lung ultrasound should start in the least dependent area of the thorax. In the supine patient this is usually over the third rib space in the mid-clavicular line. The more complete the evaluation, the higher the sensitivity of lung ultrasonography for ruling out pneumothorax; therefore, all stages of the thorax should be evaluated. Nonetheless, a limited scan of the anterior chest wall misses only isolated apical pneumothoraces according to a recent study.⁵ Extending the scan superiorly or supraclavicularly in order to better assess the apices is a reasonable option if there is a high

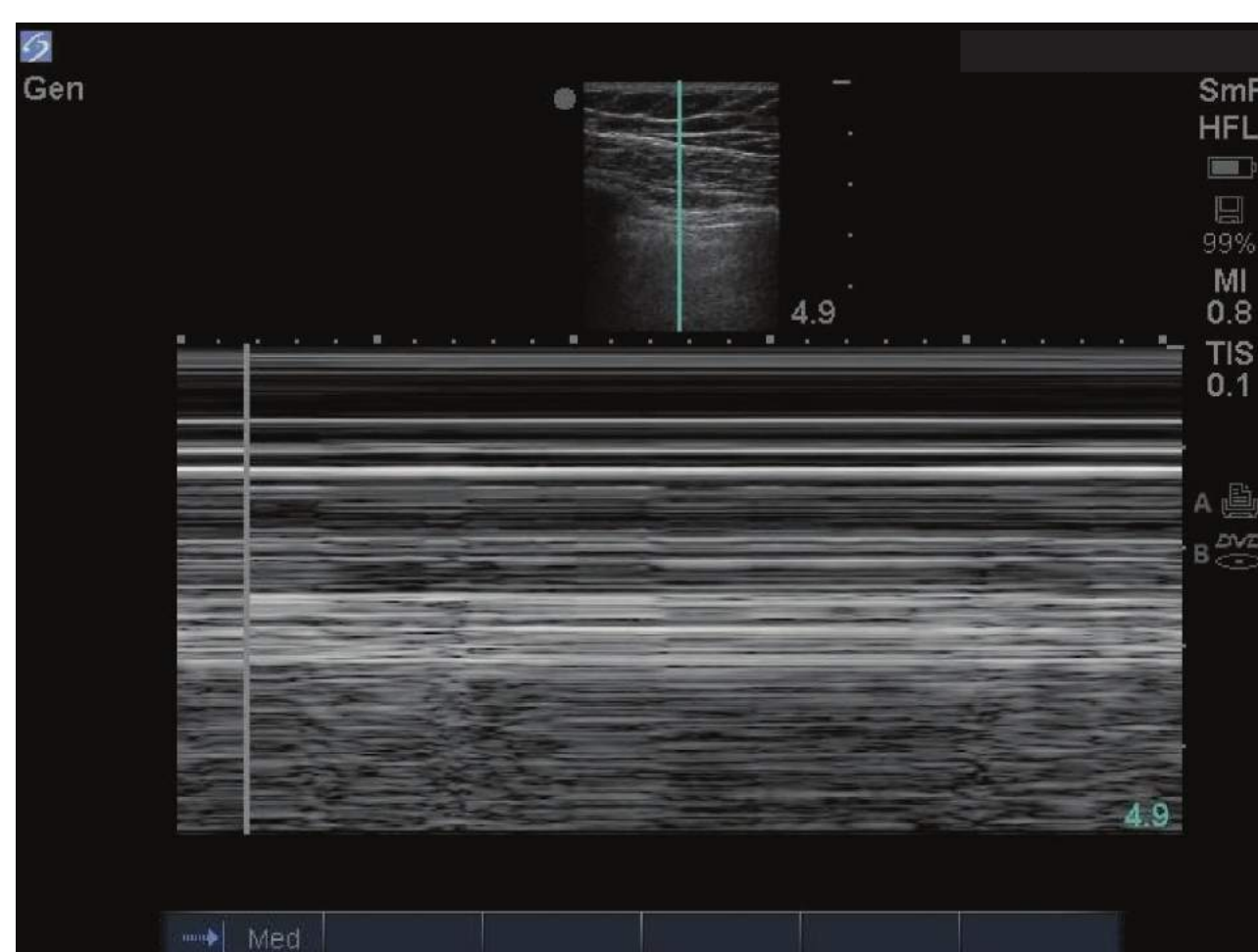


FIGURE 56-4 Pneumothorax and the stratosphere or barcode sign. Used with permission from Ashika Jain.

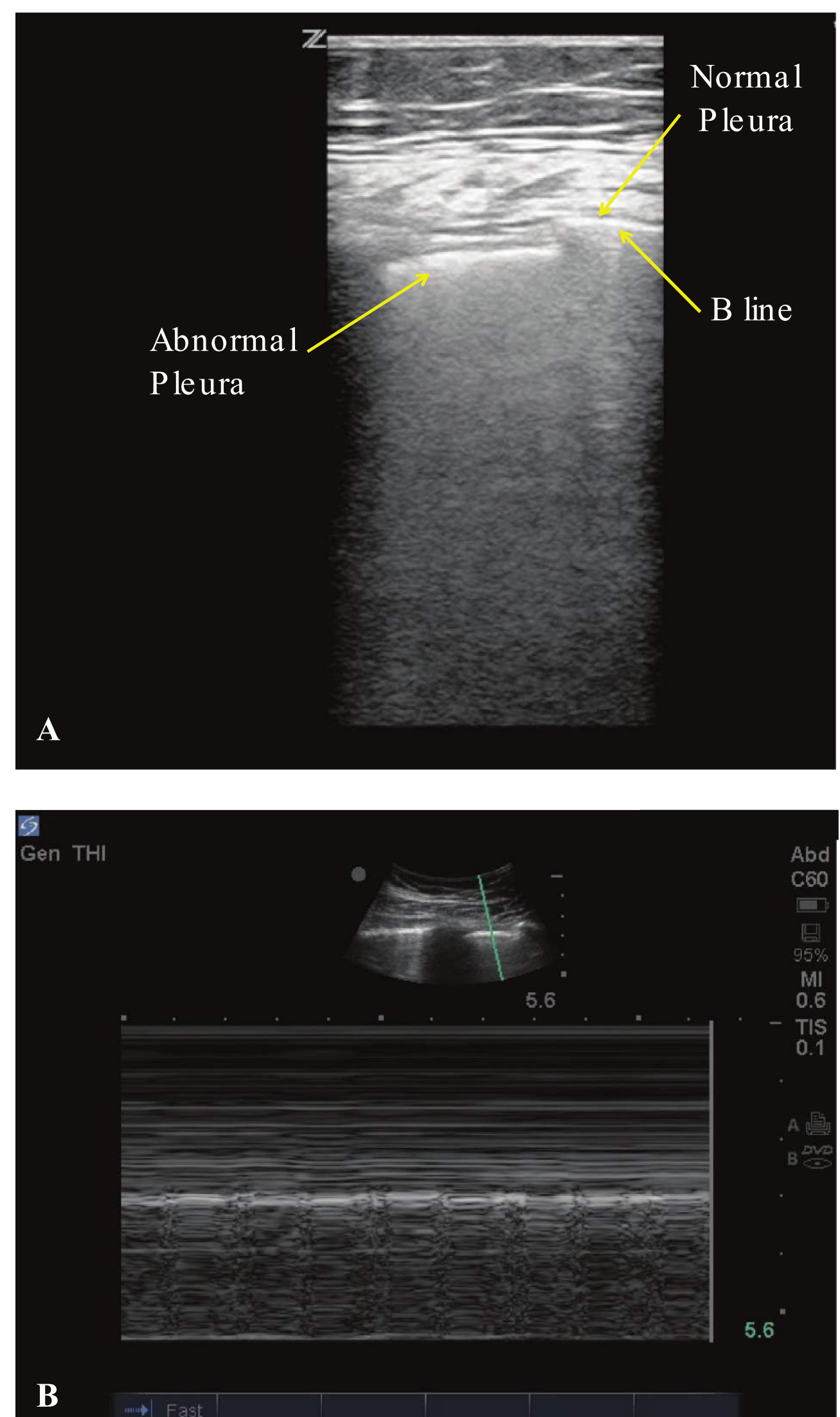


FIGURE 56-5 (A) The lung point depicted by a “break” in the smooth pleural line. (B) Lung point in M-mode as alternating barcode and seashore signs. Used with permission from Ashika Jain.

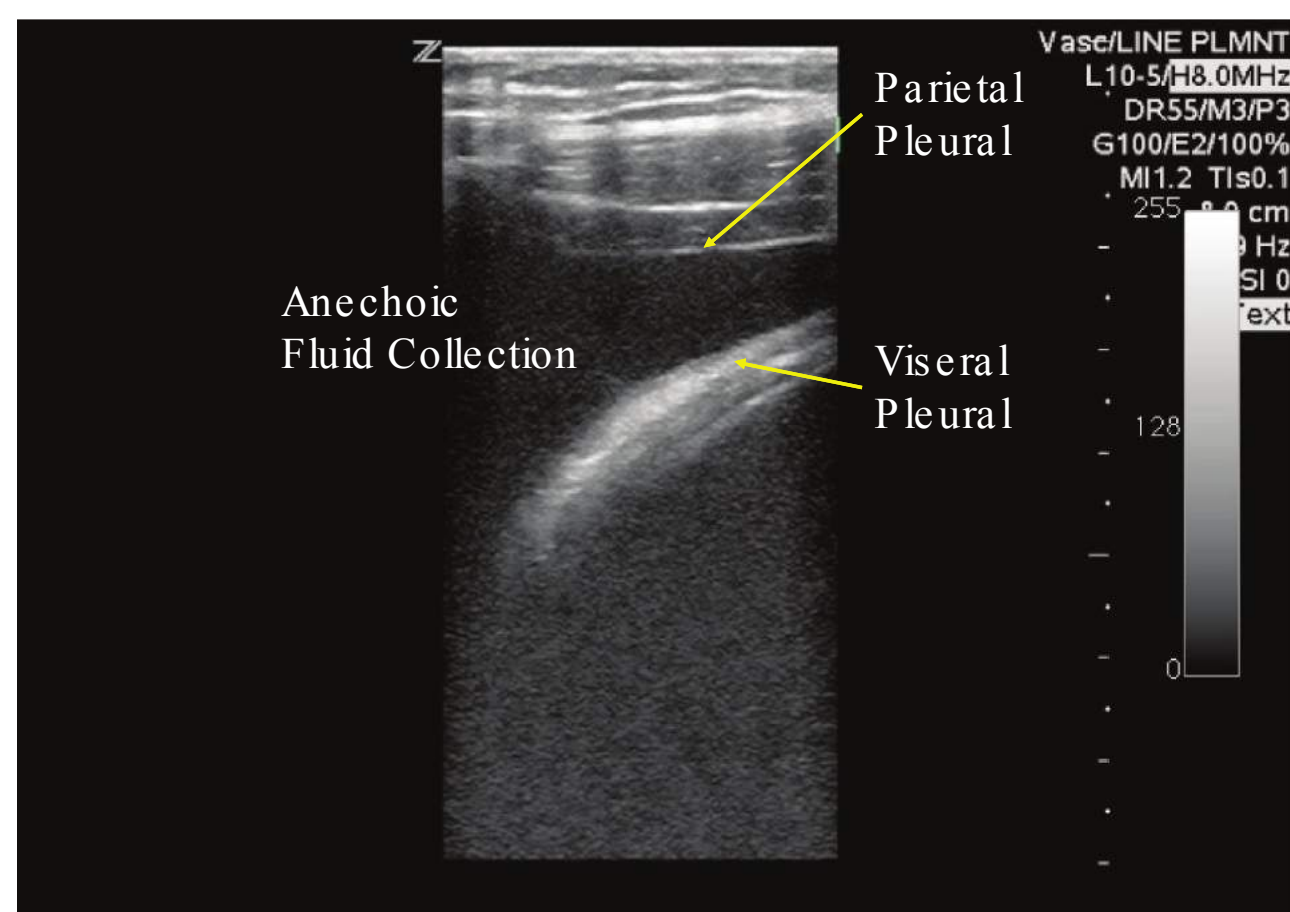


figure 56-6 Anterior pleural effusion. Used with permission from Ashika Jain.

degree of suspicion for a pneumothorax and lung sliding is identified on the anterior chest wall.

Pleural effusion

A pleural effusion appears as an anechoic space separating the parietal and visceral pleura.

When visualized on the anterior chest wall, it is defined by the parietal pleural line superiorly, the visceral pleural line inferiorly (Figure 56-6). Lung parenchyma is typically noted to move with respiration (*jellyfish sign*), and when visualized on M-mode, it rhythmically floats toward the chest wall with respiration (*sinusoid sign*).

When visualized on the lateral chest wall, it is associated with the posterolateral alveolar and/or pleural syndrome (PLAPS).

In the normal, well-aerated lung, sound waves reflect off of the diaphragm and are reflected back to the diaphragm after traveling through the liver or the spleen. The ultrasound machine assumes the sound waves travel only in a straight line; the extra time elapsed from the ultrasound waves reflecting off the diaphragm is displayed as a function of depth. As a result, liver or spleen reflections appear both above and below the diaphragm on the ultrasound screen. This is known as a *mirror image* (Figure 56-7). The presence of a mirror image rules out a dependent pleural effusion.

A pleural effusion can also be identified by the presence of the *spine sign* (Figure 56-8). Normally, visualization of the spine terminates at the diaphragm because air in the lung parenchyma refracts most of the ultrasound waves, obscuring deep structures. In the presence of pleural fluid, there is extension of this spinal stripe because the effusion provides a window to visualize deep structures. Ultrasound waves travel from the chest wall to the vertebral bodies, which appears as a scalloped line deep to the liver and spleen when looking from the mid-axillary probe position.

interstitial syndrome

Interstitial syndrome is defined as pulmonary edema (hemodynamic from fluid overload and cardiogenic; permeability-

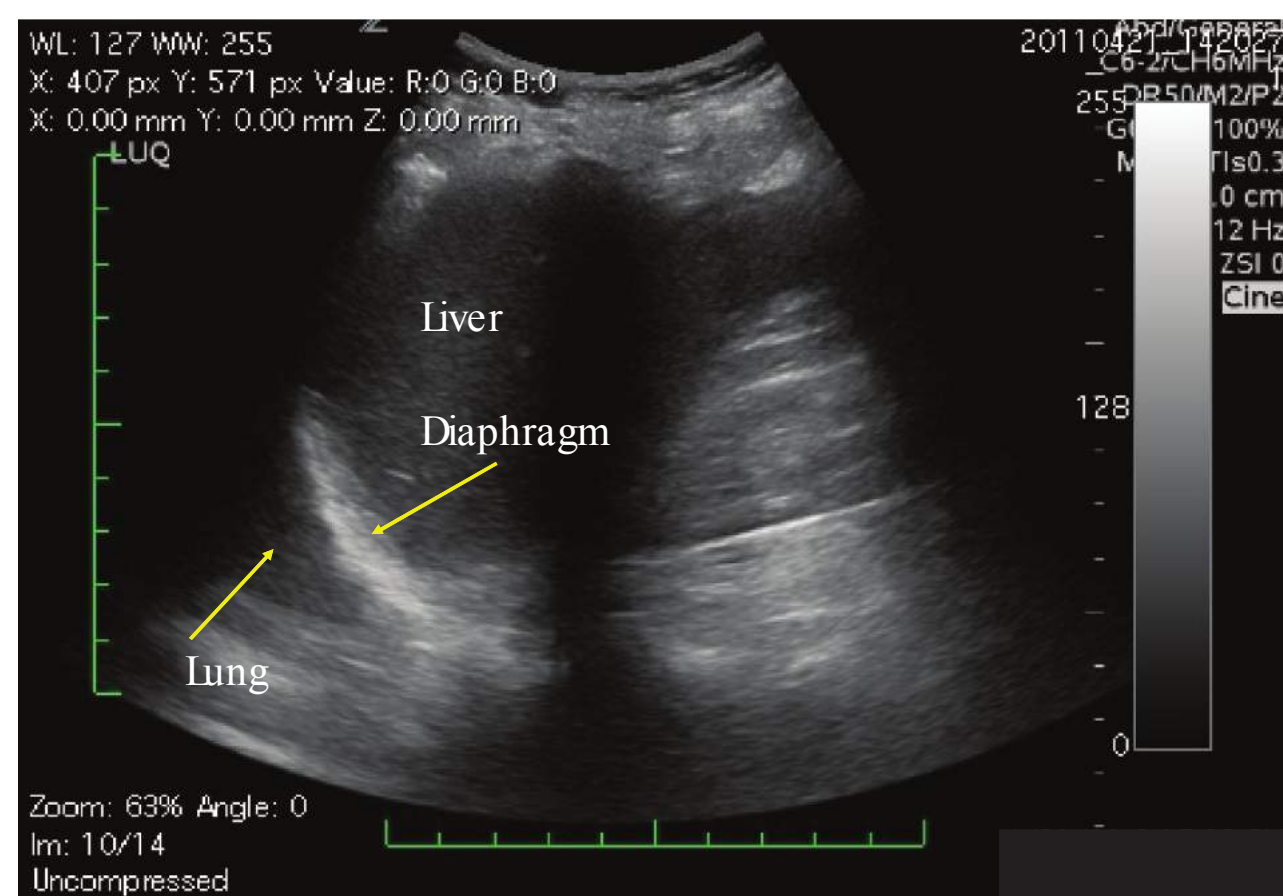


figure 56-7 Normal lung parenchyma as mirror image of the liver. Used with permission from Ashika Jain.

induced by acute respiratory distress syndrome and any inflammatory syndromes surrounding infectious processes) or chronic (usually idiopathic fibrosis).³ B-lines are a hallmark of interstitial syndrome and their amount per rib space correlates with its severity.

Ultrasound helps in distinguishing between the different etiologies of interstitial syndrome. Hemodynamic pulmonary edema is generally caused by fluid translocation; therefore, the pleural line remains thin and regular.

In contrast, permeability-induced pulmonary edema affects the pleural line as well, which becomes irregular, lumpy, and has areas of subpleural fluid collections.³

alveolar syndrome

Alveolar syndrome describes the ultrasonographic appearance of the lung when the interstitial tissue starts to consolidate, and the alveoli and air-filled space in the lung become filled with fluid or pus. In this case, sound waves are transmitted through the consolidated lung in the same way as through

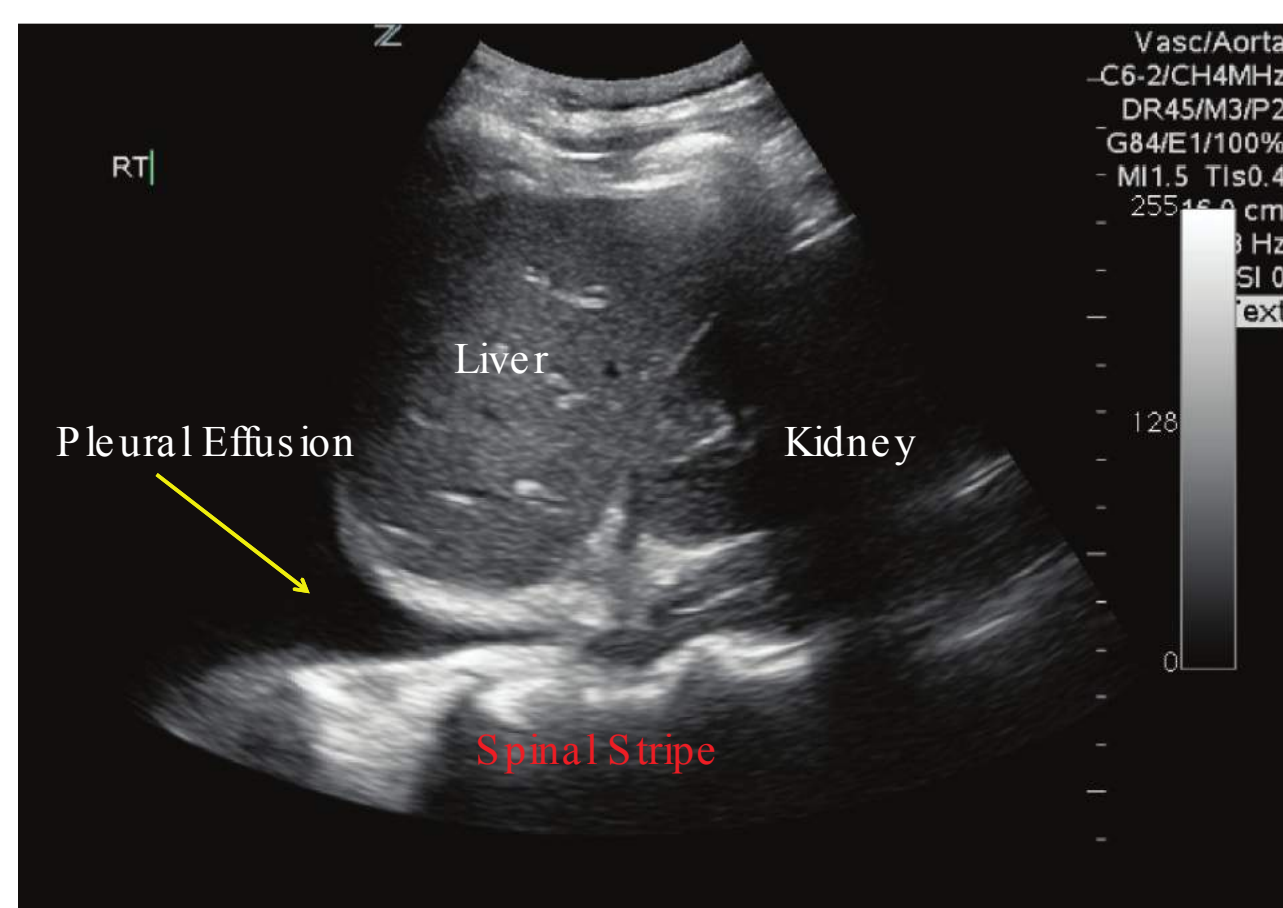


figure 56-8 Spine sign with extension of the spinal stripe superior to the diaphragm. Used with permission from Ashika Jain.

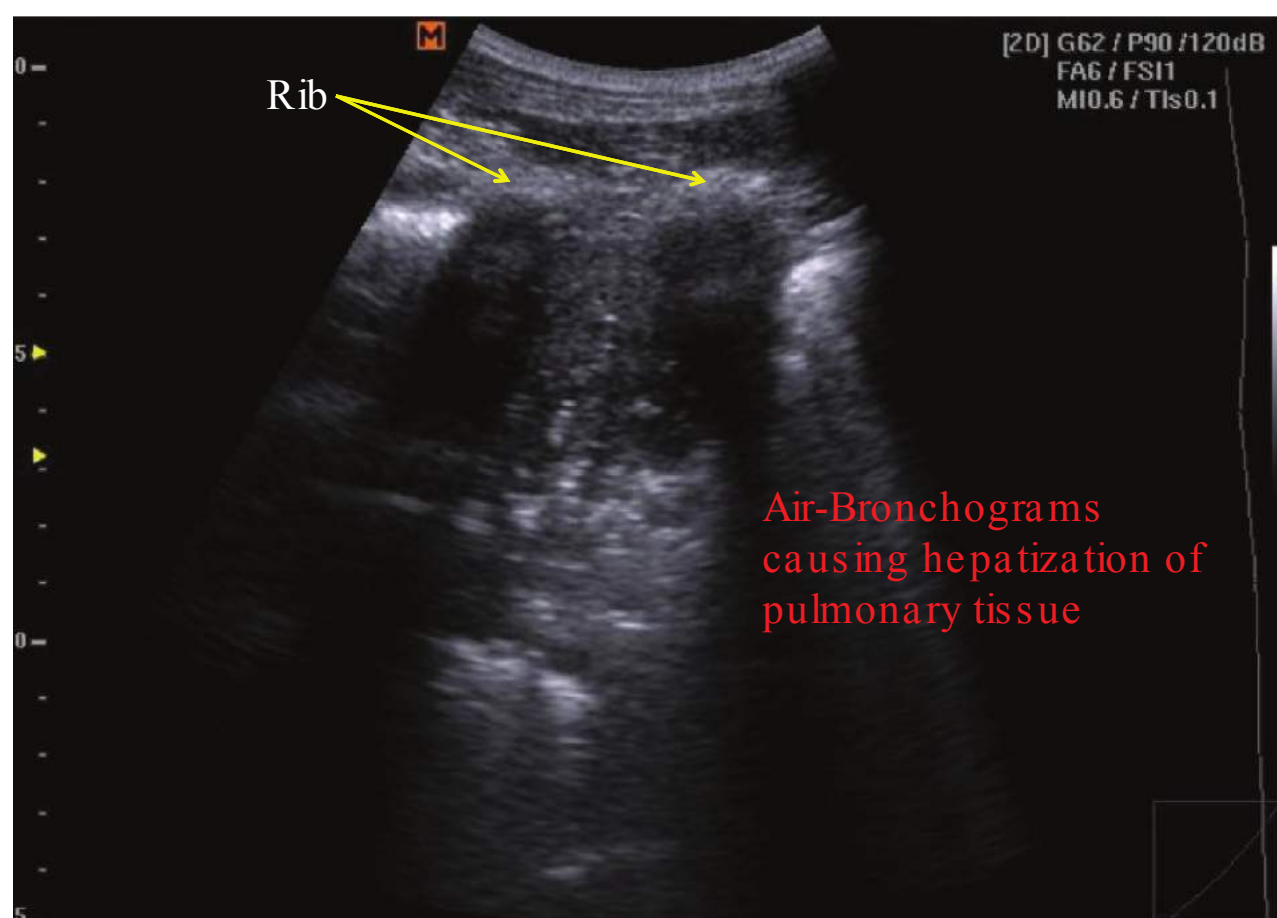


FIGURE 56-9 Hepatization or alveolar syndrome with consolidation. Used with permission from Ashika Jain.

other parenchymatous organs, such as the liver. This finding is referred to as ultrasonographic hepatization.

When compared to chest radiography, an advantage of lung ultrasonography is that it is able to differentiate between consolidation and atelectasis.

In consolidation, the bronchi are typically patent, and because of the differences in tissue densities, the air moving in the bronchi with respiration appears as a bright, shimmery column, described as mobile air bronchograms. A *shred sign*, described as shredded tissue-like pattern encompassed by the parietal pleural line, the visceral pleural line, and a deep, irregular border, can be observed (Figure 56-9).

In contrast, atelectasis is a consequence of bronchial occlusion; therefore, the air column within the consolidation does



TABLE 56-1: Lung Profiles

Profile	Meaning
A	Predominantly A-lines
B	Predominantly multiple anterior diffuse B-lines
A/B	Predominant A-lines on one side and predominant B-lines on the other side
C	Anterior alveolar consolidation(s)
PLAPS	Posterolateral alveolar and/or pleural syndrome

not move dynamically and is described as a static air bronchogram. Lung sliding is typically absent and a lung pulse can be observed.

Alveolar syndrome does not describe a specific diagnosis such as pneumonia, but rather occurs with any alveolar filling process and with atelectasis (compressive from pleural effusion or resorptive from bronchial block).

ACUTE RESPIRATORY FAILURE

In 2008, Dr. Daniel A. Lichtenstein highlighted the relevance of lung ultrasound in the diagnosis of acute respiratory failure and developed a simple algorithm named the BLUE (Bed-side Lung Ultrasound in Emergency) protocol.⁶ The different combination of A-lines, B-lines, lung sliding, anterior alveolar consolidation, and posterolateral alveolar and/or pleural syndrome is called a profile. The profiles evaluated are summarized in Table 56-1. The algorithm suggested is summarized in Figure 56-10.

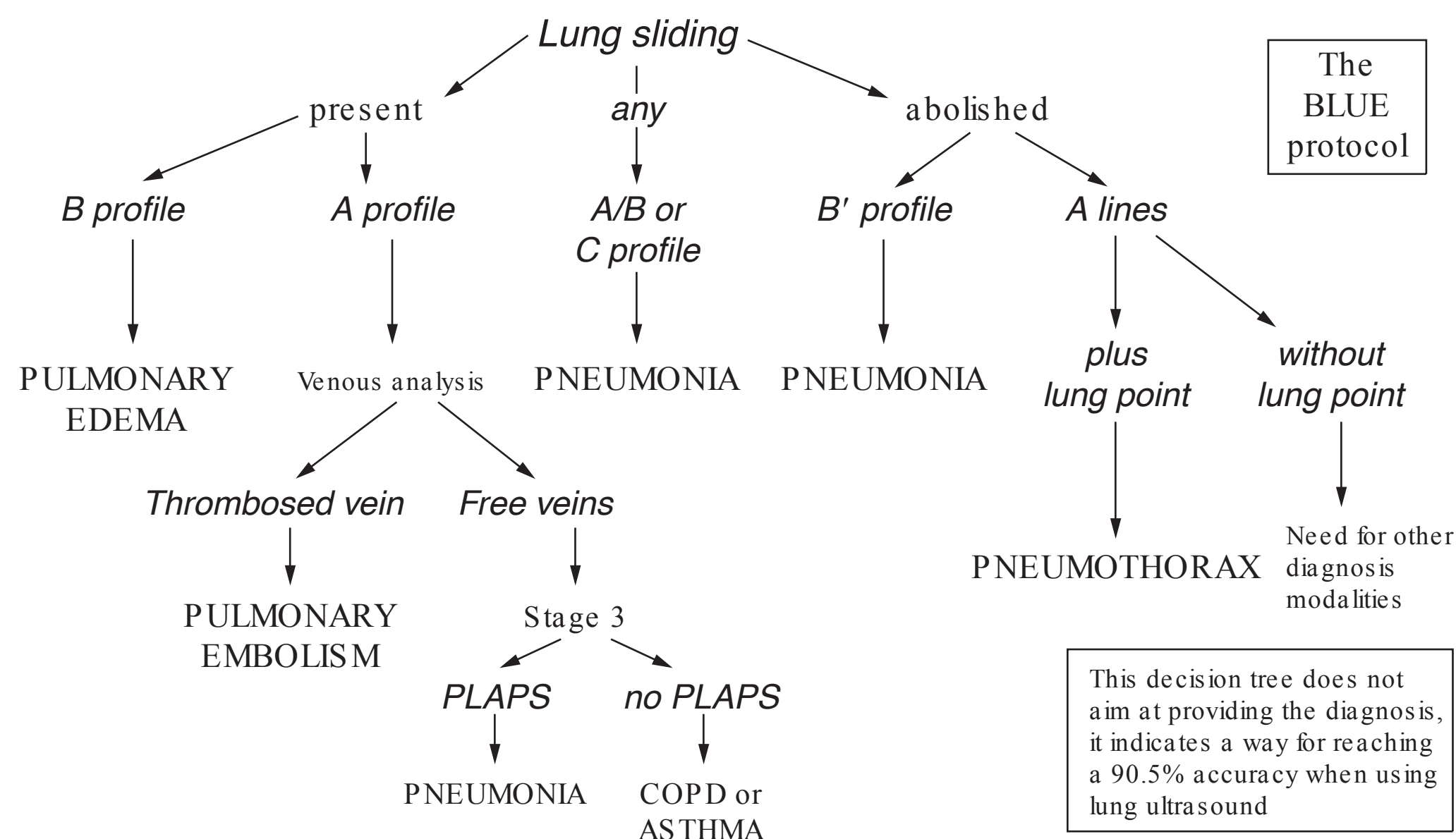


FIGURE 56-10 The BLUE Protocol. (Reproduced with permission from Lichtenstein D, Mézière G: Relevance of lung ultrasound in the diagnosis of acute respiratory failure: the BLUE protocol, *Chest* 2008 Jul;134(1):117–125.)

DYNAMIC MONITORING

Lung ultrasound findings are dynamic and change in real time with the patient's condition,⁷⁻⁹ as demonstrated by a study of dialysis patients whose B-lines resolved within hours after a dialysis session.⁸ In mechanically ventilated patients undergoing changes in positive end-expiratory pressure, consolidation and B-lines appear and disappear rapidly.⁹ Consequently, there is a growing body of evidence that ultrasonography could become the primary imaging modality of the lung, even replacing chest radiography.^{10,11}

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SPECIAL CONSIDERATIONS

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Fluid Management

Matthew T. Robinson • Alan C. Heffner

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INTRODUCTION

Relative and absolute hypovolemia complicate many clinical conditions, and fluid therapy is a cornerstone of acute critical illness management. The clinician is constantly tasked with assessment of volume status, the need for fluid therapy, and the selection of the appropriate fluid and dose guided to a suitable endpoint. Timely fluid therapy maintains macrocirculatory and microcirculatory support and reduces morbidity and mortality.^{1,2} In contrast, both under- and over-resuscitation adversely affect outcome; inadequate resuscitation risks leaving a patient in compensated shock, and overly aggressive fluid administration results in volume overload without improving oxygen delivery and is associated with worse clinical outcomes.^{3,4} A thorough understanding of the appropriate selection, timing, and goals of fluid therapy is vital to optimize patient care.

GENERAL PRINCIPLES

Fluid Distribution and Movement

Water is the most abundant constituent of the body, comprising between 50% and 70% of total body weight. Variations in total body water (TBW) depend primarily on lean body mass, since fat and other tissue contain very little water (Table 57-1). Water is distributed within both intracellular fluid (ICF) and extracellular fluid (ECF) compartments. The

distribution of water in an average adult male is shown in Table 57-2. The intracellular space contains two-thirds of the TBW, with the remainder distributed to the extracellular space, which is further divided into interstitial and intravascular spaces in a 3:1 ratio. These fluid compartments are not contiguous but may be treated as such due to similar composition and behavior.

Water freely crosses cell membranes. Osmotic forces within fluid compartments determine water distribution within the body. Intracellular and ECF environments are iso-osmolar but physiochemically distinct due to tight regulation of dissolved solutes and proteins. Membrane-bound sodium–potassium–ATPase pumps compartmentalize sodium and potassium to the extracellular and intracellular spaces, respectively. Active restriction of sodium to the extracellular space is the foundation for isotonic sodium-based resuscitation solutions.

The intravascular fluid, or plasma, differs from all other fluid compartments in that it exists as a single continuous fluid collection and contains trapped protein moieties in a higher concentration than the surrounding interstitial fluid. Plasma proteins and the endothelial glycocalyx produce the colloid oncotic pressure (COP) that favors fluid flow into the vascular space. Fluid flux across vascular endothelial membranes is governed by Starling forces (Table 57-3). In health, transcapillary hydrostatic force is nearly opposed by COP. Small net losses from the vascular space are returned to the systemic circulation via the lymphatic system. Albumin typically

 **TABLE 57-1: Total Body Water Estimates**

	TBW (%)
Adult	
Male	60
Female ^a	50
Elderly ^a	50
Obese ^a	50
Infant	70

Total body water (TBW) represents 50–60% of lean body weight in adults.
^aLower TBW proportional to skeletal muscle mass.

accounts for 80% of COP, whereas large cellular moieties such as red cells and platelets contribute less oncotic pressure effect. Increased hydrostatic pressure, hypoalbuminemia, and pathologic endothelial permeability are common clinical conditions that enhance fluid extravasation from the vascular compartment. The clinical consequences may be large, with persistent resuscitation requirements resulting in cumulative tissue edema that can adversely impact organ function. Alteration of COP and enhanced retention of intravascular volume is one theoretical advantage of colloid-based fluids.

Effective Circulating Volume

Effective circulating volume (ECV) refers to the portion of intravascular volume contributing to organ perfusion. It falls with hypovolemia but does not necessarily correlate with volume status since organ perfusion is also dependent on cardiac output (CO), arterial tone, and circulatory distribution. As an example, ECV may be compromised by limited CO despite optimized volume status.

PATHOPHYSIOLOGY

The immediate consequence of hypovolemia is impaired oxygen delivery, which triggers a swift compensatory response. CO is the most important determinant of oxygen delivery, with the flexibility to compensate for reduced oxygen-carrying capacity and/or increased metabolic demands. In the setting of hypovolemia, the body acts to defend itself through adjustments to maintain perfusion pressure and oxygen delivery (Table 57-4).

 **TABLE 57-3: Starling’s Law Governing Fluid Flux across Vascular Endothelium**

$$V = K_f [(P_{\text{capillary}} - P_{\text{interstitium}}) - \sigma(\text{COP}_{\text{capillary}} - \text{COP}_{\text{interstitium}})]$$

P, hydrostatic pressure; σ , reflection coefficient that reflects membrane permeability (value range 0–1). Inflammatory-mediated endothelial permeability reduces σ . COP, colloid oncotic pressure.

At the macrocirculatory level, volume loss leads to decreased venous return and decreased CO. Reduced stretch sensed by aortic and carotid baroreceptors leads to swift sympathetic catecholamine release, resulting in peripheral vasoconstriction, tachycardia, and enhanced cardiac contractility. These compensatory measures attempt to maintain CO in the face of a falling stroke volume. Venoconstriction shunts blood from capacitance vessels and maintains intrathoracic blood volume and cardiac preload. Organ blood flow is directly proportional to perfusion pressure in most vascular beds, and vasoconstriction maintains critical arterial pressure. Preferential perfusion simultaneously shunts limited CO to vital organs at the expense of reduced blood flow to non-critical (hepatosplanchnic, renal, cutaneous) organs. As such, mean arterial pressure (MAP) is maintained despite hypovolemia and organ hypoperfusion.

CLINICAL PRESENTATION

Signs and Symptoms

Hypovolemia primarily manifests as circulatory insufficiency. Signs and symptoms reflect organ dysfunction and the counter-regulatory response set in motion to offset the hypovolemic state. Classically, hypovolemia is portrayed to follow a step-wise progression of signs and symptoms based on the volume deficit. The clinical reality is that signs of hypovolemia are highly variable depending on the culprit disease, acuity, and individual physiologic reserve. Children and healthy adults with vigorous compensatory mechanisms may tolerate large volume loss in the absence of severe clinical symptoms. In contrast, patients with limited cardiac reserve may poorly tolerate even minimal fluid loss. Compared with hemorrhage, sepsis presents a complicated hypovolemic state in which absolute fluid deficits are compounded by pathologic vasodilation and accelerated end-organ dysfunction.

 **TABLE 57-2: Size and Composition of Body Fluid Compartments (Values Based on 70-kg Male)**

Compartment	Body Weight (%)	Volume (L)	H ₂ O (L)	Na (mmol/L)	K (mmol/L)	Cl (mmol/L)	HCO ₃ (mmol/L)
Total body	60	45	42				
ICF	40	30	28 (60%)	16	150	4	10
ECF	20	15	14 (40%)	140	4	103	26
Interstitial	16	12					
Plasma	4	3					
Blood	7	5					


TABLE 57-4: Determinants of Systemic Oxygen Delivery

Oxygen Delivery (DO_2) = Cardiac Output (CO) \times Oxygen carrying capacity (CaO_2)

DO_2		Organ Perfusion	
CO	CaO_2	Organ Blood Flow	Tissue Utilization
HR \times SV	(1) Hgb \times $\text{SpO}_2 \times 1.38$	Perfusion pressure	Microcirculatory flow
Preload	(2) $\text{PaO}_2 \times$ 0.0031	Arterial distribution	Tissue oxygen extraction
Afterload	Autoregulation	Mitochondrial function	Contractility

Delayed capillary refill, dry axilla and mucus membranes, abnormal skin turgor, and sunken eyes are classic, but imperfect, hallmarks of hypovolemia. Symptoms of reduced CO such as fatigue, dyspnea, postural dizziness, or near syncope are common but are neither specific nor sensitive. Nonfocal confusion, agitation, and lassitude are common manifestations of hypovolemia in elderly patients.⁵ Organ dysfunction can be the heralding signal of hypovolemia and may occur in the absence of global hypoperfusion or hemodynamic instability. Oliguria, concentrated urine, and increased serum creatinine are examples. Electrolyte and acid–base derangements associated with hypovolemia may also produce a constellation of associated symptoms.

Blood Pressure

Shock defines a state of inadequate tissue perfusion in which tissue oxygen delivery is inadequate to meet metabolic needs. Contrary to popular belief, the term does not reflect perfusion pressure; shock may occur with low, normal, or elevated blood pressure. Inadequate perfusion in the setting of normal blood pressure is labeled *compensated shock*. Arterial pressure is intensely preserved via compensatory vasoconstriction, and normotension often masks clinical recognition of hypoperfusion and individual severity of illness. Difficulty in identifying these patients prompted the terms *occult hypoperfusion* and *cryptic shock* to describe hemodynamically stable patients with microvascular failure. Hyperlactatemia is an important clue to identifying these patients. Increasing risk of adverse events is associated with serum lactate above the normal threshold of 2 mmol/L.⁶ Lactate > 4 mmol/L is frequently used to identify high-risk medical and trauma patients who require a coordinated resuscitation plan. The majority of critically ill patients present in compensated shock with normal or near-normal blood pressures. Left unresuscitated, these patients may progress to frank hypotension. Transient hypotension represents progressive exhaustion of cardiovascular compensation and is an important first sign of uncompensated shock that should

not be underappreciated.^{7,8} *Uncompensated shock*, characterized by hypotension, is a late finding and develops when physiologic attempts to maintain normal perfusion pressure are overwhelmed or exhausted. As such, hypotension should always be considered pathologic. MAP < 65 mm Hg, systolic blood pressure < 90 mm Hg, and/or MAP > 20 mm Hg below baseline should raise concern.^{9,10}

It is also important to understand the limitations of blood pressure measurements in critically ill patients. Automated blood pressure cuffs rely on the oscillometric method of blood pressure determination and may overestimate true arterial blood pressure in low-flow states.¹¹ Direct auscultation with reliance on Korotkoff sounds may underestimate actual systolic blood pressure by as much as 30 mm Hg in low-flow states. The potential for large measurement errors in hemodynamically unstable patients warrants consideration for invasive arterial pressure monitoring.

Heart Rate

Sinus tachycardia is nonspecific but should prompt careful clinical consideration of volume depletion, hemorrhage, and sepsis. Heart rate typically increases in the early stages of hypovolemia to maintain CO in the face of falling stroke volume. However, heart rate response to acute volume loss is highly variable. In otherwise healthy patients, volume loss of up to 20% fails to induce a tachycardic response.⁵ This compensatory response may be further blunted by comorbid disease and medications, especially β -blockers. Paradoxical and relative bradycardia occur in up to 30% of patients with traumatic and nontraumatic hemoperitoneum.^{12,13}

Orthostatic Blood Pressure

The discriminative power of postural vital signs depends on appropriate testing and integration with specific clinical findings. Reassessment of supine resting blood pressure and pulse rate should be performed at least 2 minutes after standing because all patients have a brief orthostatic response after standing. Postural pulse change > 30 beats/min is unusual in normovolemic patients.⁵ Severe postural dizziness with intolerance of the upright position confirms hypovolemia, in contrast to subjective symptoms that do not limit standing. Postural hypotension, defined as a systolic blood pressure decline of > 20 mm Hg, is seen in 10–30% of normovolemic patients. The postural hemodynamic response may also be altered due to aging and medications. Up to 30% of elderly patients demonstrate an orthostatic response in the absence of volume depletion.¹³

Shock Index

The shock index (SI) is the ratio of the heart rate to systolic blood pressure. The normal range is 0.5–0.7. SI > 0.9 identifies patients at high risk for adverse events and the need for escalated therapy across a number of diseases. In this way, the SI aids in recognizing patients with acute severe illness despite

**TABLE 57-5: Differential Diagnosis of Undifferentiated Shock and/or Hypotension**

Hypovolemia
Blood loss
Fluid loss
Gastrointestinal
Renal
Insensible
Third-space
Vasodilatory
Sepsis
Anaphylaxis
Adrenal crisis
Neurogenic shock
Toxin-/medication-induced
Obstructive/central
Cardiac dysfunction
Cardiac tamponade
Pulmonary embolus
Tension pneumothorax

deceptively normal blood pressure.¹⁴ SI identifies acute blood loss better than either HR or SBP alone.¹⁵

FLUID RESUSCITATION

Indications

Circulatory failure is the final common pathway of many diseases and carries a wide differential diagnosis (Table 57-5). Inadequate circulating volume is the most common primary etiology of shock. Immunologically mediated pathologic vasodilation compounds the fluid deficit in many clinical conditions. Acute cardiac decompensation and pulmonary embolus are two exceptional situations in which limited volume resuscitation and priority of mechanical and catecholamine resuscitation are recommended.

Volume depletion describes the state of contracted ECF with clinical implications of compromised ECV, tissue perfusion, and function. It is distinguished from *dehydration*, which implies an intracellular water deficit characterized by plasma hypernatremia and hyperosmolarity. Hypovolemia may occur as a consequence of blood, electrolyte, and/or primary water loss (Table 57-6).

Rapid restoration of underlying fluid deficit is a first step to reverse hypoperfusion in cases of overt volume depletion or undifferentiated shock. Restoration of adequate oxygen delivery through fluid resuscitation initially relies on maximizing stroke volume. After the initial resuscitation and stabilization phase, ongoing fluid replacement is tailored to specific clinical scenarios.

Intravenous Access

Appropriate intravenous access is vital to resuscitation. The determinants of flow through a rigid tube are shown in

**TABLE 57-6: Anatomic Sites of Nonhemorrhagic Volume Loss**

Gastrointestinal	Vomiting
	Diarrhea
	Drainage (e.g., ostomy, fistula, nasogastric, wound VAC)
Renal	Diuresis (e.g., medication, osmotic)
	Salt wasting
	Diabetes insipidus
Skin	Burn
	Wound
	Exfoliative rash
	Sweat
Third-space sequestration	Intestinal obstruction
	Peritonitis
	Crush injury
	Pancreatitis
	Ascites
	Pleural effusion
	Capillary leak
Insensible loss	Respiration
	Fever

Table 57-7. The rate of volume infusion is determined by the dimension of the vascular catheter and not by the size of the cannulated vein. Flow is directly proportional to the fourth power of the catheter radius and inversely proportional to the catheter length. Therefore, doubling the catheter size results in a 16-fold increase in flow, whereas doubling the cannula length decreases flow by half.

Central venous catheters (CVCs) enable hemodynamic monitoring and provide a reliable portal for volume therapy, vasoactive drug infusion, and serial blood sampling. Due to the differential catheter lengths, infusion rates through adult CVCs are up to 75% less than with peripheral catheters of equal diameter. In some circumstances, massive volume infusion may require the use of large-bore introducer (8.5–9.5 French) catheters that support flow rates approaching that of intravenous tubing at almost 1 L/min¹⁶ (Table 57-8). Additionally, manual compression of the fluid bag is an inefficient method of improving flow when compared with use of an external pressure bag.¹⁷

Endpoints of Resuscitation

Endpoints or markers of resuscitation are imperative to guide therapy during acute critical illness support (Table 57-9).

**TABLE 57-7: Determinants of Flow through a Rigid Tube**

Hagen–Poiseuille equation: $Q = (P_{in} - P_{out}) \times (\pi r^4 / 8\mu L)$

Q , flow; $P_{in} - P_{out}$, pressure gradient; μ , viscosity; L , tube length; r , radius.


TABLE 57-8: Intravenous Fluid Flow Rate through Intravenous and Central Venous Catheters

Size of Cannula	Length (mm)	Internal Diameter (mm)	Flow Rate (mL/min)
20 gauge IV	32	0.7	54
18 gauge IV	32	0.9	104
18 gauge IV	45	0.9	90
16 gauge IV	32	1.2	220
16 gauge IV	45	1.2	186
14 gauge IV	32	1.6	302
14 gauge IV	45	1.6	288
9 Fr Perc. sheath	100	2.5	838
3 mm IV tubing		3	1,030

Rapid restoration of perfusion pressure is a priority. Restoration of MAP to at least 65 mm Hg supports organ blood flow autoregulation.¹⁸ Traditional markers of blood pressure, heart rate, and urine output should be monitored during resuscitation, but no single marker guarantees adequate oxygen delivery or organ perfusion.^{1,9,10} Resuscitation aimed to these markers risks leaving the patient in persistent compensated shock.

Resuscitation aims to stabilize oxygen delivery to meet global and regional metabolic requirements. Serum lactate and central venous oxygen saturation (ScvO₂) have emerged as rapid, reliable markers of physiologic stress and global perfusion.

Admission lactate and base deficit (BD) predict morbidity and mortality independent of hemodynamics.^{6,19} These markers of illness severity are conversely useful as endpoints of resuscitation. Rapid lactate clearance over the first hours of care is associated with improved outcome in critical illness and should be incorporated into goals of resuscitation.^{20–22} Initial BD often correlates with serum lactate, but serial measures are confounded by underlying disease (e.g., renal insufficiency, malnutrition), resuscitation fluid (e.g., normal saline induced acidosis), and other therapies (e.g., bicarbonate, blood products).

ScvO₂ reflects the systemic balance of oxygen delivery and utilization. Decreased oxygen delivery is compensated by increased tissue oxygen extraction, resulting in a fall in ScvO₂ below the normal 70%. ScvO₂ is a practical bedside measurement that is sampled from a catheter (CVC or PICC) positioned in the superior vena cava. Although subnormal ScvO₂ is associated with adverse outcome, sepsis trials targeting this endpoint show mixed results.^{23–25} As such, systematic central venous cannulation to measure this endpoint in the absence of another indication is not endorsed, although it represents a pragmatic measure when access is available. In contrast to lactate kinetics, ScvO₂ response is rapid and dynamic, such that monitoring provides immediate feedback on resuscitation efforts (or clinical deterioration).


TABLE 57-9: Prioritized Endpoints of Fluid Therapy

1. Adequate intravenous access
2. Mean arterial pressure > 65 mm Hg
3. Optimized oxygen delivery and organ perfusion
 - a. Systemic markers
 - Serum lactate clearance (> 5%/hr) and normalization
 - b. Regional markers
 - Cutaneous temperature and perfusion
 - Urine output > 0.5 mL/kg/hr

The optimal endpoint of resuscitation remains controversial. We cannot expect a single resuscitation endpoint to perform in all clinical circumstances. As such, a multimodal approach seeking to normalize a combination of both global and regional perfusion markers as quickly as possible is most prudent (Table 57-9).

THE VOLUME CHALLENGE

The goal of fluid resuscitation is intravascular expansion to optimize stroke volume. The empiric volume challenge remains the standard means of early fluid resuscitation. Volume expansion is achieved by infusing serial aliquots of isotonic fluid under direct observation. The use of crystalloid (10–20 mL/kg) or colloid (5–10 mL/kg) is infused quickly over 15–20 minutes, and serial boluses are titrated to the clinical endpoint objective while monitoring for adverse effects. A positive clinical response to volume loading confirms volume responsiveness but does not predict further response to therapy. This can contribute to overly aggressive volume expansion.

Total volume requirements are difficult to predict at the onset of resuscitation and are often underestimated. Classic hypovolemia that occurs with acute hemorrhage or fluid loss may stabilize rapidly with appropriate volume expansion. The 3:1 rule of hemorrhage resuscitation suggests that 3 volumetric unit of crystalloid are required to replete the ECF deficit of 1 unit of blood loss. However, experimental models confirm the experience in severely traumatized patients whose fluid requirements exceed the 3:1 suggestion.²⁶ Pathologic vasodilation and transcapillary leak contribute to the need for ongoing volume replacement. Crystalloid requirements average 40–60 mL/kg in the first hour of septic shock but may be as high as 200 mL/kg to normalize perfusion.²⁷

VOLUME RESPONSIVENESS

Volume or preload responsiveness refers to the ability to augment stroke volume with fluid administration. *In contrast to the empiric volume challenge, volume responsiveness is gauged prior to fluid administration with the information used to guide whether fluid administration is part of the solution to reverse clinical hypoperfusion.* Fluid loading in nonresponsive patients

should be avoided because it delays appropriate therapy and contributes to volume overload and organ dysfunction, including hypoxemic respiratory failure and abdominal compartment syndrome.

Predicting Volume Responsiveness

The primary reason to administer a fluid challenge is to augment stroke volume and oxygen delivery. Although empiric volume challenges are frequently used in clinical medicine, up to 50% of critically ill patients fail to improve cardiac output with ongoing fluid administration following initial resuscitation.²⁸

Volume or preload responsiveness refers to the potential for fluid administration to augment stroke volume. *In contrast to the empiric volume challenge, volume responsiveness is gauged prior to fluid administration, and the information is used to guide whether fluid administration is part of the solution to reverse clinical hypoperfusion.*

Fluid loading in volume unresponsive patients should be avoided because it delays appropriate therapy and contributes to fluid excess with organ dysfunction, including hypoxemic respiratory failure and abdominal compartment syndrome. In the absence of persistent clinical hypovolemia, a more rational approach for patients who remain hypoperfused after initial empiric volume therapy > 60 mL/kg incorporates selection and titration of subsequent therapy under the guidance of objective cardiovascular monitoring.

Clinical examination and vital signs are unreliable predictors of volume responsiveness. As such, invasive hemodynamic measurements are frequently used as surrogates of preload and predictors of volume responsiveness. CVP monitoring in the critically ill is an established practice that has been widely advocated as a surrogate for preload, with absolute or change in CVP (Δ CVP) used to predict volume responsiveness. In the absence of conflicting data, a target CVP of 8–12 mm Hg is often recommended to optimize preload prior to the institution of pressor and inotropic support.

Unfortunately, cardiac pressure surrogates of preload reflect the net influences of intravascular volume, venous tone, cardiac function, and intrathoracic pressure. These myriad influences confound their ability to reflect intravascular volume status or preload responsiveness of an individual patient.^{29–31} There is no consistent threshold CVP to reliably estimate response to fluid administration.^{32,33} Values that are considered low, normal, or high can be found in patients who respond positively to fluid. Obstructive lung disease, positive pressure ventilation, myocardial dysfunction, reflex venoconstriction, and erroneous measurements are several examples that can result in elevated CVP in a volume-responsive patient. CVP rise coupled to clinical improvement with volume loading corroborates fluid responsiveness but does not anticipate further effect.

Volumetric measures of preload including stroke volume, right and global end-diastolic volume, and left ventricular end-diastolic area can be obtained with several monitoring techniques. These volumetric surrogates of preload are intuitively more desirable, but they, too, have limited predictive

value because discriminatory thresholds are imprecise and infrequent in clinical practice.³¹ Serial volumetric data in response to therapy may assist in individual patient management, but the dynamic nature of cardiovascular function during critical illness confounds data interpretation.

Dynamic Indices of Fluid Responsiveness

Fluid responsiveness is best predicted by dynamic indices of preload reserve. Respiratory variation in stroke volume during positive pressure mechanical ventilation is among the most reliable signs of preload responsiveness.^{29,31} Positive pressure ventilation induces cyclic alteration in preload. A resulting variation of systolic pressure, pulse pressure, and stroke volume > 13% identifies patients capable of augmenting stroke volume in response to fluid administration. A regular (preferably sinus) rhythm, positive pressure ventilation on > 8 mL/kg tidal volume, and absence of significant patient interaction with the ventilator are important requirements for interpretation of these data.

Passive leg raising (PLR) is a provocative maneuver that tests whether a reversible volume challenge results in improved stroke volume.³⁴ This is an attractive option since it provides immediate information to guide therapy without the administration of potentially unnecessary fluid. PLR results in the translocation of venous blood from the lower extremities to the thorax. The transient increase in preload improves stroke volume within minutes. Rapid feedback stroke volume measurement tools are required to identify the brief response to PLR. Sensitivity and specificity of PLR in predicting volume responsiveness is > 95% in a wide variety of patients, including ventilated and spontaneously breathing patients and in those with irregular cardiac rhythms.³⁵ The use of a mini-fluid bolus (approximately 100–250 mL) while assessing the cardiac indices pre- and post-infusion provides may provide similar information as a PLR.³⁶

Focused bedside ultrasound to determine global cardiac function and measure respirophasic change in the vena cava (IVC) provide insight into cardiac performance and volume responsiveness. Respirophasic collapse of the IVC > 50% during spontaneous breathing is often used as an indicator of volume responsiveness, but a clear threshold to discriminate fluid responsiveness remains incompletely defined.^{37–39}

FLUID SELECTION

Early resuscitation and replacement of fluid deficits may be performed using a variety of available choices. Each possesses specific benefits and disadvantages, such that insight into fluid composition is important for clinical care (Tables 57-10 and 57-11). There is growing evidence that the choice of resuscitation fluid may affect patient outcomes. Trials incorporating restrictive fluid strategies also provide evidence for goal-directed fluid use to specific endpoints to avoid unnecessary fluid administration and avoid adverse consequences of positive fluid balance.^{30,40–42}



TABLE 57-10: Intravenous Fluid Composition and Distribution

Solution	Electrolytes (mEq/L)							mOsm/L	pH	Distribution	
	Na	K	Ca	Mg	Cl	HCO ₃	Lactate			ECF	ICF
Crystalloid											
0.9% NaCl	154				154			308	5	100%	
Ringer's lactate	130	4	3		109		28	273	6.5		
150 mEq NaHCO ₃ (three ampoules) in 1 L water	130					130		260			
3% NaCl	513				513			1,027	5		
7.5% NaCl								2,400			
0.45% NaCl	77				77			154	5	67%	33%
0.20% NaCl	34				34			77	5		
D ₅ W								278	4	33%	67%
Normosol-R	140	5		3	98	27 acetate 23 gluconate		294	7.4		
Plasmalyte	140	5		3	98	27 acetate 23 gluconate		294	7.4		

Crystalloid

Isotonic sodium-based crystalloids preferentially distribute to the extracellular compartment, which includes the vascular space. A 1 liter infusion of isotonic crystalloid distributes approximately one quarter into the vascular compartment. This is the basis for the 3:1 rule often cited for resuscitation in acute hemorrhagic shock. The ratio more closely approximates 7:1 or 10:1 in severe hemorrhage due to decreased COP secondary to hemorrhage, capillary leak, and crystalloid replacement. Interstitial tissue edema is the cost of such high-volume crystalloid requirement.

Fluid selection appears less important than volume dosage titrated to an appropriate therapeutic endpoint. 0.9% Normal saline (NS) and lactated Ringer's (LR) are the two most commonly used isotonic resuscitation solutions. Evidence of clinical superiority for either was historically lacking, and the source of hypovolemia, associated electrolyte derangements, and volume requirements are important determinants

of fluid selection. NS supplies a supraphysiologic sodium and chloride load that induces hyperchloremic metabolic acidosis when administered in large volumes. This may be advantageous to correct volume and electrolyte disturbances in cases of metabolic alkalosis due to loss of gastric secretions (e.g., vomiting, gastric outlet obstruction, NG suctioning). However, the supraphysiologic concentration of chloride is proinflammatory and induces renal vasoconstriction associated with acute kidney injury, coagulopathy, and adverse outcomes compared to balanced salt solutions.^{43–47}

Crystalloids with a chemical composition that more closely approximates ECF, termed *balanced salt solutions*, have gained recent attention and are increasingly advocated as first-line resuscitation fluids.⁴⁰ LR, or Hartmann's solution, was originally introduced in the 1930s by adding sodium lactate as a buffer to Ringer's solution for the treatment of metabolic acidosis. It is a more physiologic fluid, containing potassium and calcium in concentrations near plasma levels. Due to its more physiologic pH, it is preferred in large-volume resuscitation.



TABLE 57-11: Composition of Colloid Solutions

Solution	Na	Cl	K	Ca	Lactate	Colloid	Average MW (Da)	pH	mOsm/L	OP (mm Hg)
5% albumin	130–160	130–160				Human Albumin (50 g/L)	70,000	6.6	290	20
25% albumin	130–160	130–160				Human Albumin (250 g/L)	70,000	6.6	310	100
Hetastarch										
Hespan®	154	154	4			HES 60	600,000	5.9	310	30
Hextend®	143	124			28	HES 60	670,000	5.9	307	30
Voluven®	154	154				HES 60	130,000	4.0–5.5	308	36–37
Volulyte	137	110	4		34	HES	600,000	5.7–6.5	286	

Electrolyte concentration in mEq/L. MW, molecular weight; OP, oncotic pressure.

One caution is that calcium within the solution can bind to medications and the citrated blood anticoagulant, making it an incompatible transfusion fluid.

Colloids

Colloid solutions are composed of electrolyte preparations fortified with large-molecular-weight molecules (MW > 30,000). The presence of these large molecules contributes to total oncotic pressure, which favors retention of fluid within the vascular space. The ideal colloid solution has an oncotic pressure similar to plasma, which permits replacement of the plasma volume without distribution to other fluid compartments. The net effect and theoretical benefit of colloid infusion is intravascular expansion without accompanying expansion of the interstitial compartment.

The potency of colloid solutions on plasma expansion differs with individual fluids. Higher COP provides greater expansion of the plasma volume. Albumin, dextran, and blood are naturally occurring colloids, whereas synthetic colloids include modified gelatins, hydroxyethyl starch (HES), and hemoglobin solutions. Albumin is the only colloid that contains molecules of uniform weight. Other colloid solutions are composed of polymers with a wide variety of molecular sizes. The average molecular weight of a colloid solution is an unreliable indicator of intravascular persistence, and molecular weight distribution curves provide the best indicator of intravascular effect.

Vascular retention of colloids makes them efficient volume expanders. Although equally effective when titrated to the same clinical endpoints, crystalloid solutions require two to four times more volume for equivalent resuscitation. Colloids therefore restore intravascular volume and tissue perfusion more rapidly if access and administration rate are limited. Furthermore, dilutional hypoalbuminemia, transcapillary fluid shift, and interstitial and pulmonary edema are limited.

Historically, use of synthetic colloids was associated with a variety of complications, including renal dysfunction, coagulopathy, and hypersensitivity reactions. New-generation HES aimed to improve this profile. Unfortunately, recent large-scale trials have consistently demonstrated dose-dependent nephrotoxicity and adverse outcomes associated with the use of HES.^{48,49} Pending further data, there is no current safe dose or indication for use of synthetic colloids for resuscitation.

Albumin

Human albumin is a single polypeptide solution derived from pooled human serum albumin and is available in 5% and 25% concentrations. Five percent albumin is iso-oncotic to plasma, with > 70% of infused volume retained within the vascular space. Hyperoncotic albumin (25% albumin) was initially developed in the 1940s for combat resuscitation. Infusions of hyperoncotic albumin result in vascular expansion greater than two times the administered volume.⁵⁰ In addition to the obvious benefits of small-volume resuscitation, improved portability, and more rapid hemodynamic

stabilization, hyperoncotic albumin has additional advantages. Synergistic interaction with administered drugs and primary antioxidant effects are hypothesized explanations for the improved morbidity and mortality linked to hyperoncotic albumin for complicated hypoalbuminemic states including decompensated end-stage liver disease.^{51,52} Increased COP mobilizes interstitial edema, and the effects of hyperoncotic albumin are relatively long-lasting, persisting for up to 12 hours after infusion. As such, hyperoncotic albumin is often matched with loop diuretic therapy to mobilize fluid in volume-overloaded patients.⁵³

Albumin appears safe in critical illness but does not provide consistent outcome advantage over crystalloids.^{54,55} However, use in specific patient subgroups has important implications. Early albumin use may confer benefit in patients with severe sepsis.⁵⁶ Albumin also improves organ function and morbidity and is superior to crystalloids for intravascular volume expansion during hemodialysis, following large-volume paracentesis, and in combination with antibiotic therapy for spontaneous bacterial peritonitis.^{57,58} Traumatic brain injury remains an important exception in which isotonic albumin is associated with increased risk of adverse outcome compared with crystalloid resuscitation, with a significant increase of mortality noted in the population.⁵⁹

Hypertonic Saline

Hypertonic sodium (HS) solutions, with sodium concentrations ranging from 3% to 7.5%, rapidly expand intravascular volume by mobilizing water from interstitial and intracellular spaces. Small infusions expand plasma by several times the infused volume without resultant expansion of the interstitial fluid space and edema seen with crystalloid infusions.⁶⁰ Additional benefits include improved cardiovascular performance secondary to positive inotropic effects and microvascular vasodilation, improved microcirculatory flow, and attenuation of the inflammatory response. HS is safe, but there are insufficient data to conclude that hypertonic saline is better than isotonic crystalloid for the resuscitation of patients with burns, trauma, or sepsis. Multitrauma patients with traumatic brain injury remain the most common indication for HS, but outcome benefit also remains equivocal in this group.^{61,62}

SPECIAL CIRCUMSTANCES

Minimal Volume Resuscitation of Hemorrhagic Shock

Hemorrhagic shock poses a unique challenge between balancing the timing and type of resuscitation in relation to the achievement of hemostasis. On one hand, hypotensive patients should be stabilized with rapid fluid infusion to maintain perfusion to essential organs. However, overly aggressive fluid resuscitation before control of bleeding may result in increased blood loss and mortality.⁶³ Factors that prevent hemostatic plug formation and allow renewed bleeding, such as increased volume and blood pressure, decreased



TABLE 57-12: Sources of Life-Threatening Hemorrhage to Consider a Strategy of Limited Volume Resuscitation Pending Surgical Bleeding Control

Penetrating torso trauma
Ruptured aortic aneurysm
Major hemothorax
Major hemoperitoneum
Traumatic aortic injury
Severe pelvic fracture
Gastrointestinal bleeding
Ectopic pregnancy
Postpartum hemorrhage

blood viscosity, and dilution of clotting factors, are all associated with fluid resuscitation.

Strategic, limited volume resuscitation re-emerged in the 1980s as the value of early prehospital resuscitation in penetrating trauma was questioned. A prospective trial comparing immediate and delayed fluid resuscitation in hypotensive patients with penetrating torso injuries showed improved mortality, fewer complications, and a shorter hospital length of stay with delayed resuscitation.^{64,65} Limited prehospital resuscitation with judicious use of fluids may offer the optimal approach, with conventional resuscitation ensuing after surgical hemostasis is achieved.⁶⁶ The degree and duration of permissive hypotension remains unclear, although current recommendations target SBP of 70 mm Hg. Patients with concomitant brain injury are not candidates for this strategy (Table 57-12).

Burn Resuscitation

Patients with second- and third-degree burns exhibit marked fluid shifts related to denuded skin, injured tissue, and systemic inflammatory response. Aggressive fluid resuscitation is necessary to restore intravascular volume and maintain end-organ perfusion. Early anticipation of these large fluid requirements prevents underresuscitation. Initial fluid requirements are most commonly calculated according to the Parkland formula (Table 57-13).

Formula calculations are based on the time of injury as opposed to the time to medical attention and should incorporate prehospital fluid administration. LR is the preferred crystalloid solution. Several formulas exist, but no single method is clearly superior.⁶⁷ All formulas are intended to provide an initial *guide* for resuscitation requirements. Actual fluid needs may vary significantly, necessitating modifications based on individual status.⁶⁸ Strict adherence to a calculated goal may result in over- or under-resuscitation. Over-resuscitation is common and contributes to increased pulmonary complications and morbidity. Maintenance fluid requirements should be allocated in addition to burn formula replacement. Urine output > 1 mL/kg/h is a traditional endpoint of acute burn



TABLE 57-13: Parkland Burn Resuscitation Formula to Guide Acute Fluid Therapy

Parkland formula:

24-hour fluid requirement = 4 mL × weight (kg) × body surface area burn (%)

First 1/2 of fluid calculation administered over the first 8 h from injury

Second 1/2 of fluid calculation administered over the subsequent 16 h

Maintenance fluid calculations should be added to burn resuscitation estimates

Burn formulas estimate fluid requirements over the initial 24 h of burn therapy

Volume requirements may substantially exceed formula approximation

resuscitation and may be augmented by the perfusion endpoints discussed earlier.

MAINTENANCE FLUID THERAPY

In contrast to resuscitation therapy, the goal of maintenance fluid therapy is normal body fluid composition and volume. Fluid orders anticipate daily fluid requirements, ongoing losses, and coexisting electrolyte abnormalities. Although often ordered concurrently, daily physiologic fluid estimate (true maintenance) should be consciously distinguished from therapy aimed to slowly replace an existing fluid deficit.

Routine water and electrolyte maintenance are based on normal energy expenditure, sensible loss from urine and stool, and insensible loss from the respiratory tract and skin. Calculations assume euvolemia and are adjusted for body mass (Table 57-14). Greater per kilogram fluid requirements in children are proportionate to TBW and metabolism. All maintenance prescriptions should be individualized: energy expenditure, fluid losses, and electrolyte status vary with disease and dictate rate and electrolyte modifications. For example, exfoliative skin disease, increased work of breathing, and



TABLE 57-14: Maintenance Fluid Estimate

Body Weight (kg)	Daily Maintenance (mL/day)	Hourly Maintenance (mL/h)
1–10	100 mL/kg	5 mL/kg/h
10–20	1,000 mL plus 50 mL/kg	40 mL/h plus 2 mL/kg/h
20–80	1,500 mL plus 20 mL/kg ^a	60 mL/h plus 1 mL/kg/h ^a

Sodium and chloride: 2–3 mEq per 100 mL water. Potassium: 1–2 mEq per 100 mL water. D5 1/4 normal saline with 20 mEq KCl is a common maintenance solution for most euvolemic pediatric patients and provides 20% of daily calories at routine maintenance rate. Comorbid conditions and/or electrolyte abnormalities may require modification.

^aTo maximum 2,400 mL/day or 100 mL/h.

fever enhance insensible loss. Measurable nasogastric, fistula, ostomy, and urinary drainage can be estimated or replaced by drainage volume. Limitation of fluid and potassium is an important disease-specific modification for patients with renal insufficiency.

Hypotonic solutions with or without dextrose and potassium are popular fixed-combination maintenance solutions. Hospitalized patients often suffer impaired free water excretion due to nonosmotic antidiuretic hormone (ADH) release, making them vulnerable to hyponatremia. Serum sodium concentration provides a simple and accurate marker of hydration status. Isotonic maintenance solutions should be considered in patients (including children), especially those with serum sodium < 138 mEq/L.^{69–71} Glucose infusions are best formulated by adding dextrose to an electrolyte solution (e.g., LR, NS, 0.45 NS) rather than using 5% dextrose (D₅W), which behaves as electrolyte free water on sugar metabolism.

KEY TEACHING POINTS

1. The critical window to reverse organ hypoperfusion is measured in hours, emphasizing the need for rapid recognition and correction of shock.
2. The majority of ED patients who require resuscitation present in compensated shock with normal blood pressure.
3. Early recognition of circulatory insufficiency must be coupled with timely resuscitation to impact patients.
4. Normalization of vital signs does not ensure adequate systemic perfusion or completion of resuscitation.
5. The clinical endpoint used to guide dosage of fluid resuscitation is more important than the individual product (i.e., crystalloid vs. colloid) selection.
6. Overly aggressive fluid resuscitation and positive fluid balance negatively impact patient morbidity.
7. Dynamic markers of volume responsiveness are important guides for fluid therapy.

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Nutrition Support in Critical Care

Colleen Casey

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- GUIDELINES FOR SPECIFIC DISEASE STATES 612

Nutrition support is a significant component of patient care for hospitalized patients, particularly in the critical care setting. Critical illness is often characterized by a hyper-metabolic and systemic inflammatory response including increased infectious morbidity, increased length of hospital stay, multiorgan dysfunction, and, finally, increased mortality. Historically, nutrition has been a secondary or supportive part of the care for critically ill patients with the goals of preserving lean body mass, maintaining immune function, and averting metabolic complications of critical illness (blunting the catabolic effect of critical illness). Recently, these goals have evolved to focus on applying nutrition as a therapy, with current goals being to attenuate metabolic response to stress, prevent oxidative cellular injury, and favorably modulate immune response.^{1,2} The importance of nutrition support as a therapy is becoming more readily apparent with advances in evidence-based medicine. However, there are many factors to consider when determining an appropriate comprehensive nutrition therapy plan for each critically ill patient.

Consulting a registered dietitian or nutrition support team for expert care is paramount to maximizing nutrition support and its associated benefits for the critically ill patient. Early involvement of these practitioners in patient care allows for management of aspects of nutrition support as large in scope as meeting macronutrient needs (the necessary calorie and protein provision for recovery) to the finest nuances of micronutrient, vitamin, and mineral provision. The nutrition support practitioner adjusts the nutrition support regimen throughout the changing and, at times, complex course of the critically ill patient. He or she tailors the frequency of intervention and reassessment to meet the needs of each individual patient as the patient progresses through critical illness.

ASSESSMENT OF NUTRITION STATUS

Assessment of nutrition status involves several components:

- Subjective information
- Anthropometrics
- Physical exam
- Laboratory values
- Etiology-based approach to support the diagnosis of malnutrition
- Calculation of calorie and protein requirements

Subjective information can include, but is not limited to, diet and weight history, social history as it relates to nutrient intake, chronic diseases that may alter nutrient intake, absorption, and utilization, and use of medications. Physical assessment will include subjective global assessment of the patient.

Anthropometrics not only gives us a sense of one's weight in relation to height by determining ideal body weight (IBW) and body mass index (BMI), but also helps us begin to determine our patient's nutritional state by revealing if one is overweight, obese, or with baseline malnutrition (see Table 58-1). Determination of IBW and %IBW is important in the formulation of nutrition therapy goals because they are applied to many predictive equations commonly utilized in critical care to estimate patients' calorie and protein requirements.

The Hamwi method is a common and practical method of determining IBW³:

- Male: 106 lb for first 5 ft in height, plus 6 lb for each additional inch of height.
- Female: 100 lb for first 5 ft in height, plus 5 lb for each additional inch of height.

TABLE 58-1: Malnutrition Classification

Malnutrition Classification	IBW Assessment (%)	BMI Assessment
Severe malnutrition	< 69	< 16
Moderate malnutrition	70–79	16–17
Mild malnutrition	80–90	17–18.5
Normal weight	91–110	18.5–24.9
Overweight	111–129	25–29.9
Obese	≥ 130	≥ 30
Class I obesity/mild obesity		30–34.9
Class II obesity/moderate obesity		35–39.9
Class III obesity/severe obesity		≥ 40

Some additional factors to consider when determining IBW of critically ill patients include amputations (Figure 58-1) and history of spinal cord injury⁴⁻⁷:

- Paraplegia: IBW = Metropolitan Life Insurance height and weight table value with 5–10% subtracted.
- Quadriplegia: IBW = Metropolitan Life Insurance height and weight table value with 10–15% subtracted.

BMI is determined by the following formula: weight (kg)/height² (m²).

Laboratory Values

Laboratory assessment can help determine whether there is organ system dysfunction, overall fluid imbalance, and/or micronutrient or macronutrient deficiencies when utilized in conjunction with overall assessment of the critically ill patient. Some serum protein values commonly obtained in the critical care setting include the negative acute-phase reactants albumin and prealbumin and positive acute-phase reactant C-reactive protein. In healthy individuals, visceral proteins albumin and prealbumin serve as markers of nutritional status. However, albumin and prealbumin are primarily synthesized in the liver during times of anabolism, thus becoming better markers of inflammation and severity of illness than of nutritional status in the critically ill.

Additionally, albumin is not an ideal marker of nutrition status in an acute care setting due to its relatively lengthy half-life of approximately 20 days. Albumin may be increased by dehydration. It may be decreased by liver disease, protein-losing enteropathy/nephropathy, third-spacing (ascites, anasarca, effusions, burns), hemodilution, acute catabolic states (stress, trauma, infections, burns, surgery), and/or malignancy.

Prealbumin has a 2- to 3-day half-life. It can increase by as much as 4 mg/dL within 8 days with adequate nutrition support.⁸ However, prealbumin is additionally impacted and increased by renal failure, corticosteroid use, pregnancy, and alcoholism (associated with acute abuse). It is decreased by liver disease (cirrhosis), protein-losing enteropathy/nephropathy,

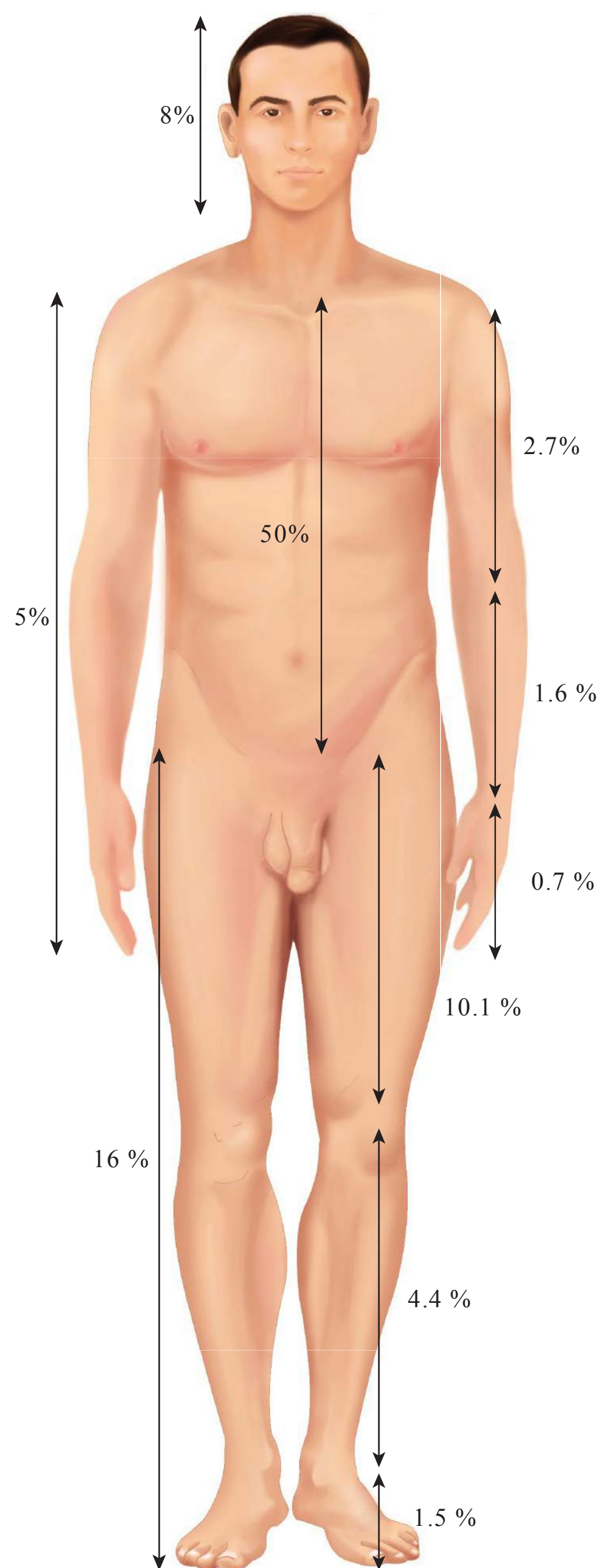


FIGURE 58-1 IBW adjustment for amputations.

nephrotic syndrome, hemorrhage, acute catabolic states (stress, trauma, infections, burns, surgery), and/or malignancy to name a few factors.

C-reactive protein is elevated by inflammation. Thus, it is a useful tool to assess the overall status of a critically ill patient when prealbumin and/or albumin are not normalizing with the provision of presumably adequate nutrition support in the absence of any known stressors just listed. An elevated C-reactive protein value indicates that prealbumin and albumin continue to be markers of the inflammatory state of illness rather than nutritional status.

A nitrogen balance study can offer an alternative means of assessing protein needs when traditional serum protein markers (such as albumin and prealbumin) are not clinically relevant. It determines the amount of nitrogen necessary to maintain nitrogen equilibrium by assessing urinary losses in a 24-hour urine collection. Urinary urea nitrogen reflects muscle catabolism, hence lean body mass. However, in the critical care population, nitrogen balance is typically negative for up to 3 weeks post-insult or post-injury due to overall stress response.

Requirements for an accurate study include:

- Creatinine clearance > 50 mL/min
- 24-Hour urine collection for urine urea nitrogen (UUN)
- Measured creatinine clearance (from urine sample) may be obtained and compared with a calculated creatinine clearance to evaluate the validity of the urine sample and urea nitrogen result.

Factors impacting outcome include:

- Tendency to overestimate intake (i.e., if nutrition intake inaccurately recorded)
- Underestimating losses (i.e., unquantified gastrointestinal losses or losses from chest tubes or wounds drains)
- Not considering specific amino acid source (l-arginine provides 5.1 g protein to 1 g nitrogen)
- Renal insufficiency
- Inadequate urine collection
- Possible hematuria

Goals for nitrogen balance may include:

- Equilibrium – 1 to + 1
- Anabolism + 2 to + 4
- Decreased negative nitrogen balance (when anabolism not possible for critically ill patient):

Nitrogen balance = nitrogen intake – nitrogen losses

$$\text{Nitrogen balance} = \left[\frac{\text{protein (g per day)}}{6.25} \right] - [\text{UUN (g per day)} + 4^*]$$

The following assumptions should be applied to the preceding formula:

- $\text{UUN (g per day)} = \left[\frac{\text{UNN (mg/dL)}}{100} \right] \times \text{urine (L per day)}$
- Non-UUN = ~1–2 g
- Fecal nitrogen = ~1–2 g
- Miscellaneous losses from desquamation of skin, epithelial surfaces, sweat, etc. = ~1 g
- UUN > 30 (g/24 hours) uses a factor of + 6 insensible losses (patients with extraordinary losses)
- *Typical factor = + 4 (*routine insensible losses*)

Using a nitrogen balance study, one would increase protein delivery by 6.25 g for each gram of nitrogen under

desired balance. However, clinical status may prevent protein increase to meet desired balance in patients with organ dysfunction or fluid restrictions.^{9,10}

Etiology-Based Approach to Support the Diagnosis of Malnutrition

The Academy of Nutrition and Dietetics (AND) and the American Society for Parenteral and Enteral Nutrition (ASPEN) have combined efforts and developed a consensus for defining malnutrition in adults in clinical care settings. This recent approach describes two levels of malnutrition:

- severe protein calorie malnutrition
- malnutrition of moderate degree (non-severe)

This includes the three typical etiologies:

- acute illness/injury: severe acute inflammation (< 1 month)
- chronic illness: mild to moderate chronic inflammation (> 1 month)
- social/environmental circumstances: without inflammation

Six main characteristics:

- insufficient energy intake
- weight loss
- loss of subcutaneous fat intake
- loss of muscle intake
- localized or generalized fluid accumulation
- diminished functional status (measured by hand-grip strength)

A minimum of two of the listed characteristics is recommended for the diagnosis of malnutrition of severe or non-severe malnutrition. Characteristics are described in detail in Table 58-2.¹¹

Calculation of Calorie and Protein Requirements

Calculation of energy requirements most often involves the use of indirect calorimetry, predictive equations, or kilocalories per kilogram calculations. For purposes of this section, the terms calorie and kilocalorie are equivalent.

Indirect calorimetry is the “gold standard” for determining calorie requirements in the critically ill and is the standard against which predictive equations are compared. It is particularly useful in determining caloric needs in complex patient populations such as trauma, burns, obesity, sepsis, cancer, prolonged mechanical ventilation, amputations, patients with unreliable anthropometrics, COPD, major surgical procedure, acute pancreatitis, hypermetabolism/hypometabolism, paralysis/quadruplegia, and failure to respond to nutrition therapy.

Indirect calorimetry measures oxygen consumption (Vo_2) and carbon dioxide production (Vco_2):

- Respiratory quotient (RQ) can be calculated by dividing Vco_2 by Vo_2 .

 **TABLE 58-2: Academy/ASPEN Clinical Characteristics That the Registered Dietitian Can Obtain and Document to Support the Diagnosis of Malnutrition in Adults**

Food and Nutrition Intake. (Kondrup, 2001). Malnutrition is the result of inadequate food and nutrient intake or assimilation; thus, recent intake compared with estimated requirements is a primary criterion defining malnutrition. The RD obtains or reviews the food and nutrition history, estimates optimum energy needs, compares energy needs with estimates of energy consumed, and reports inadequate intake as a percentage of estimated energy requirements over time.

Malnutrition in the Context of Acute Illness or Injury		Malnutrition in the Context of Chronic illness		Malnutrition in the Context of Social or Environmental Circumstances	
Non-severe (Moderate) Malnutrition	Severe Malnutrition	Non-severe (Moderate) Malnutrition	Severe Malnutrition	Non-severe (Moderate) Malnutrition	Severe Malnutrition
< 75% of estimated energy requirement for > 7 days	≤ 50% of estimated energy requirement for ≥ 5 days	< 75% of estimated energy requirement for ≥ 1 month	≤ 75% of estimated energy requirement for ≥ 1 month	< 75% of estimated energy requirement for ≥ 3 months	≤ 50% of estimated energy requirement for ≥ 1 month

Interpretation of Weight Loss (Blackburn, 1977; Klein, 1997; Rosenbaum, 2000; Keys, 1948). The RD evaluates weight in light of other clinical findings, including the presence of underhydration or overhydration. The RD assesses weight change over time reported as a percentage of weight lost from baseline.

% Time	% Time	% Time	% Time	% Time	% Time
1–2%: 1 week	> 2%: 1 week	5%: 1 month	> 5%: 1 month	5%: 1 month	> 5%: 1 month
5%: 1 month	> 5%: 1 month	7.5%: 3 months	> 7.5%: 3 months	7.5%: 3 month	> 7.5%: 3 months
7.5%: 3 months	> 7.5%: 3 months	10%: 6 months	> 10%: 6 months	10%: 6 months	> 10%: 6 months
		20%: 1 year	> 20%: 1 year	20%: 1 year	> 20%: 1 year

Physical findings (Keys, 1948; Detsky, 1987). Malnutrition typically results in changes to the physical exam. The RD may perform a physical exam and document any one of the physical exam findings below as an indicator of malnutrition.

Body fat. Loss of subcutaneous fat (e.g., orbital, triceps, fat overlying the ribs).

Mild	Moderate	Mild	Severe	Mild	Severe
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Muscle Mass. Muscle loss, for example, wasting of the temples (temporalis muscle); clavicles (pectoralis and deltoids); shoulders (deltoids); interosseous muscles; scapula (latissimus dorsi, trapezius, deltoids); thigh (quadriceps); and calf (gastrocnemius).

Mild	Moderate	Mild	Severe	Mild	Severe
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Fluid Accumulation. The RD evaluates generalized or localized fluid accumulation evident on exam (extremities, vulvar/scrotal edema or ascites). Weight loss is often masked by generalized fluid retention (edema), and weight gain may be observed.

Mild	Moderate to severe	Mild	Severe	Mild	Severe
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Reduced grip strength (Norman, 2011). Consult standards supplied by the manufacturer of the measurement device.

N/a	Not recommended in ICU	N/a	Measurably reduced for age/gender	N/a	Measurably reduced for age/gender
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- Resting energy expenditure (REE) is calculated by the abbreviated Weir equation:

$$REE = 3.9(\text{Vo}_2) \text{ [L per day]} + 1.1(\text{Vco}_2) \text{ [L per day]}$$

Factors impacting the accuracy of indirect calorimetry include:

- Inspired oxygen ($\text{Fio}_2 > 60\%$)
- Air leaks (endotracheal tube cuff, chest tube, broncho-pulmonary fistula)
- Hemodialysis (HD) (loss of CO_2 via dialysis coil)
- Metabolic acidosis (increases Vco_2 and alters RQ)
- Disconnection from ventilator results in hypoxemia, bradycardia, or any other adverse effect
- Canopy inappropriate for patient (i.e., claustrophobia)
- Obtaining readings in a non-steady state (Table 58-3)

 **TABLE 58-3: Traditional Interpretation of Respiratory Quotients (RQ)**

Substrate Utilization	RQ
Lipogenesis	1.0–1.2
Carbohydrate	0.9
Protein	0.82
Mixed substrate	0.85
Lipolysis	0.7
Ketosis	< 0.7
Non-steady state hyperventilation	> 1.0
Non-steady state hypoventilation	0.7
Alcohol	0.67
Starvation	0.65–0.67

An RQ of 0.8–0.95 is indicative of a patient utilizing a mixed fuel or receiving an appropriate calorie provision for maintenance of current state. However, it is important to note that for malnourished critically ill or unstable patients, overall status may prevent increasing calorie provision for repletion. Maintenance may be the only feasible and desirable acute goal.^{12–15}

For patients or institutions where indirect calorimetry is not feasible, practical, or available, predictive equations provide a widely utilized alternative. There are more than 200 predictive equations.^{1,2} A systemic review summarized by Frankenfield et al. evaluated seven commonly utilized equations with validation studies and the Fick method.¹⁶ The review included some more commonly utilized equations: Harris–Benedict equation, Harris–Benedict equation (with injury and activity factors), Ireton–Jones equation (1992 version), Ireton–Jones equation (1997 version), Penn State equation (1998 version), Penn State equation (2003 version), and Swinamer equation. The accuracy of all predictive equations is affected by the individuals making up the patient population to which they are applied, and no single equation can be applied to all critical care patients. In the critically ill obese patient, use of Penn State University 2010 equation for patients ≤ 60 years old is recommended with a high evidence grade for determining maintenance calorie needs.¹⁷

Perhaps the simplest of calculations to determine calorie goals is kilocalories per kilogram calculations. In guidelines jointly established by the Society for Critical Care Medicine (SCCM) and American Society for Parenteral and Enteral Nutrition (ASPEN) in 2009, this method was reviewed, and the recommendation of providing 25–30 kcal/kg per day in enterally fed nonobese critically ill patients received a Grade E recommendation.^{1,2,18} In the critically ill obese patient, hypocaloric enteral feeding (providing calories less than measured or estimated calorie needs while ensuring adequate protein provision) was recommended with a goal of meeting 60–70% of measured calorie requirements. Alternatively, in the absence of indirect calorimetry, 11–14 kcal/kg actual body weight or 22–25 kcal/kg IBW and ≥ 2.0 g/kg IBW of protein for Class I and Class II obesity (BMI 30–40) was recommended. For Class III obesity (BMI > 40), ≥ 2.5 g/kg IBW of protein was recommended. This recommendation received a Grade D recommendation with the rationale or goal being to yield weight loss while maintaining nitrogen balance (Table 58-4).^{1,2} More recent review of the literature results in a low evidence grade supporting improved clinical outcomes for obese hospitalized patients receiving hypocaloric, high-protein regimens (meeting 50–70% of estimated calorie needs or < 14 kcal/kg actual weight) with the recommendation or need for a large randomized controlled study noted.¹⁷

Protein is the most important macronutrient in the critical care setting for wound healing, maintaining lean body mass, and immune function. In nonobese patients (BMI < 30), the recommendation to meet these goals is 1.2–2 g/kg protein per day with needs further escalating in significantly catabolic states such as burns and trauma. This recommendation received a Grade E rating.^{1,2}



TABLE 58-4: Grading System Used for SCCM/ASPEN Guideline

Grade of Recommendation

- A: supported by at least two Level I investigations
- B: supported by one Level I investigation
- C: supported by Level II investigations only
- D: supported by at least two Level III investigations
- E: supported by Level IV or V evidence

Level of Evidence

- I: large, randomized trials with clear-cut results; low risk of false-positive (α) error or false-negative (β) error
- II: small, randomized trials with uncertain results; moderate to high risk of false-positive (α) and/or false-negative (β) error
- III: nonrandomized, contemporaneous controls
- IV: nonrandomized, historical controls
- V: case series, uncontrolled studies, and expert opinion

Large studies warranting Level I evidence are defined as those with greater than or equal to 100 patients or those which fulfilled endpoint criteria determined by power analysis. Meta-analyses were used to organize information and draw conclusions about overall treatment effect from multiple studies on a particular subject. The grade of recommendation, however, was based on the level of evidence of the individual studies.

ROUTE OF NUTRITION SUPPORT

Enteral Nutrition

Enteral nutrition (EN) is the preferred route of nutrition support over parenteral nutrition (PN). Few studies show an effect on mortality; however, the most commonly seen benefit is reduction in infectious morbidity (when comparing EN and PN). Additional benefits include reduced length of hospital stay, decreased cost of nutrition support,^{1,2,19} and return of cognitive function in brain injury.^{1,2,20}

EN should be initiated within 24–48 hours of admission and advanced toward goal in the following 48–72 hours.^{1,2,21} The rationale is that early initiation of enteral feedings is associated with decreased gut permeability and beneficial modulation of the body's immune and inflammatory responses to insult. It should also be noted that enteral feeding protocols increase percentage of goal calories delivered to the patient, with a Grade C recommendation for implementing these types of protocols. While trickle feeding may prevent intestinal atrophy, an overall goal of receiving > 50 –65% of calorie goal during the first week of hospitalization is warranted to achieve other ICU goals for nutrition support (maintaining lean body mass, etc.). The SCCM/ASPEN guideline gives the latter goal a Grade C recommendation.^{1,2}

EN should be deferred in the hemodynamically unstable patient until stabilization or resuscitation is achieved due to potential for subclinical intestinal ischemia/reperfusion injury, although less than 1% actually results in ischemic bowel. Consideration for gastric or small intestinal feeding with caution is appropriate in patients with stabilizing or tapering pressors in conjunction with ongoing GI and abdominal assessment.^{1,2,22}

Both gastric and small bowel enteral feeding are appropriate in the ICU setting, with the exception of small bowel feeding being recommended for patients with known intolerance of gastric feedings or at high aspiration risk. Three meta-analyses found no difference in mortality when comparing gastric and postpyloric feeding in the ICU with only one of the meta-analyses showing a significantly lower rate of ventilator-associated pneumonia with postpyloric feeding. This difference was attributed to the inclusion of one study that was excluded from the remaining two meta-analyses.^{1,2}

Real or perceived high gastric residuals may be an additional reason to pursue postpyloric feeding if the finding results in tube feeding being held. Holding EN for gastric residuals < 500 mL is not warranted in the absence of additional GI symptoms of intolerance and may contribute to ileus resulting from cumulative NPO time. There is no correlation between gastric residual volume and incidence of aspiration, regurgitation, or overall gastric emptying.^{1,2,23–27}

Elevating the head of the bed 30–45 degrees in all intubated enterally fed patients and utilizing prokinetic agents or narcotic antagonists are additional measures that can be taken to reduce aspiration risk.^{1,2,28,29} Erythromycin and metoclopramide have been shown to improve gastric emptying but have little effect on overall patient outcomes. Naloxone was shown to decrease gastric residual volume, increase total EN received, and decrease incidence of ventilator-associated pneumonia in one study.³⁰

Blue food coloring and glucose oxidase strips should not be used in the critical care setting to assess for aspiration. Blue dye is an insensitive marker and associated with mitochondrial toxicity and patient death in the critical care setting. The US Food and Drug Administration issued a mandate against the use of blue food coloring as a marker for aspiration of EN in September 2003. Glucose oxidase strips have poor sensitivity/specificity because they rely on the inaccurate notion that glucose in tracheal secretions is exclusively from aspirated EN.^{1,2,31}

The presence of bowel sounds is not necessary for the initiation of enteral feeding. Bowel sounds are only indicative of contractility and do not relate to mucosal integrity, barrier function, or digestive/absorptive capacity. Perceived presence of bowel sounds is variable among care providers and can be unnoticed due to noise from patient care equipment and other individuals at the bedside. Evidence shows that 70–85% of ICU patients can reach and tolerate EN goals within 72 hours of admission when enteral feeding protocols are utilized (regardless of the presence of bowel sounds, flatus, or stool).^{1,2}

In planning enteral formula selection, use of immunomodulating formulas should be considered in burns, trauma, head and neck cancer, major elective surgery, and critically ill mechanically ventilated patients, with caution in severe sepsis.^{1,2} Immunomodulating formulas are supplemented with a variety of combinations of omega-3 fatty acids, arginine, glutamine, antioxidants, and ribonucleotides. The overall outcomes on meta-analyses reveal decreased length of hospital stay, decreased duration of mechanical ventilation, and

decreased infectious morbidity in the appropriate patient populations.^{1,2,32,33} The initial hypothesis that arginine-enhanced formulations may increase patient risk by increasing nitric oxide production in severe sepsis is not widely supported. Arginine is now considered safe in mild to moderate sepsis, with caution in severe sepsis.^{1,2,34} Immunomodulating formulas are not recommended for indiscriminate use due to increased financial expense of these formulas and decreased effect on outcomes outside of the targeted patient groups just listed. Formulas with anti-inflammatory lipid profiles (omega-3 fish oils and borage oil) combined with antioxidants in acute respiratory distress syndrome (ARDS) and acute lung injury (ALI) are recommended due to significantly reduced length of ICU stay, duration of mechanical ventilation, organ failure, and mortality. At least 50–65% of goal calories should be received from immunomodulating formulas to achieve the preceding benefits.^{1,2,19,20,35–37}

Enteral formulas containing soluble fiber or small peptide formulas should be considered in the presence of ongoing diarrhea when infectious causes (*C. difficile*) and hyperosmolar agents (medications) have been eliminated (Table 58-5).^{1,2,38}

Parenteral Nutrition

PN should only be considered for use when EN is not an option. When evaluating the ICU population as a whole, the SCCM/ASPEN guideline recommends no PN even if EN is not feasible or available in the first 7 days of admission (Grade C). In the previously well-nourished patient population, PN is recommended only after the first 7 days without the option of EN (Grade E). In patients with evidence of protein calorie malnutrition, PN should be initiated as soon as possible following admission and adequate resuscitation when EN is not an option. (Protein calorie malnutrition was typically defined as loss of at least 10–15% of recent usual weight, or being < 90% of IBW [Grade C].) The preceding recommendations regarding the ICU population as a whole and the well-nourished portion of the ICU are based on two major meta-analyses that found overall reduced infectious morbidity and complications when patients were left without nutrition support and a significant increase in mortality when PN was initiated within the first 7 days. Adverse clinical outcomes increase when patients remain > 7 days without nutrition support or PN. The same meta-analyses showed reversed findings for the protein calorie malnourished group in the first 7 days (increased complications and risk of mortality).

The SCCM/ASPEN guideline goes on to state a consensus that if a patient is to undergo major upper GI surgery and EN is not an option, then PN should be initiated under very specific circumstances:

- The malnourished patient should receive PN 5–7 days preoperatively and therapy should continue postoperatively.
- In well-nourished patients, PN should be delayed 5–7 days postoperatively.


TABLE 58-5: Osmolality (mOsm/kg) of Some Liquid Medications

Commercially Available Product	Average Osmolality
Acetaminophen elixir, 65 mg/mL	5,400
Acetaminophen/codeine elixir	4,700
Amantadine HCl solution, 10 mg/mL	3,900
Aminophylline liquid, 21 mg/mL	450
Amoxicillin suspension, 25 mg/mL	1,541
Amoxicillin suspension, 50 mg/mL	2,250
Ampicillin suspension, 50 mg/mL	2,250
Cephalexin suspension, 50 mg/mL	1,950
Cimetidine solution, 60 mg/dL	5,550
Co-trimoxazole suspension	2,200
Dexamethasone Intensol solution, 1 mg/mL	3,100
Digoxin elixir, 50 µg/mL	1,350
Diphenhydramine HCl elixir, 2.5 mg/mL	850
Diphenoxylate/atropine suspension	8,800
Docusate sodium syrup, 3.3 mg/mL	3,900
Erythromycin ethyl succinate suspension, 40 mg/mL	1,750
Ferrous sulfate liquid, 60 mg/mL	4,700
Furosemide solution, 10 mg/mL	2,050
Haloperidol concentrate, 2 mg/mL	500
Hydroxyzine HCl syrup, 2 mg/mL	4,450
Kaolin-pectin suspension	900
Lactulose syrup, 0.67 g/mL	3,600
Magnesium citrate solution	1,000
Milk of magnesia suspension	1,250
Multivitamin liquid	5,700
Nystatin suspension, 100,000 U/mL	3,300
Phenytoin sodium suspension, 25 mg/mL	1,500
Promethazine HCl syrup, 1.25 mg/mL	3,500
Sodium citrate liquid	2,050
Sodium phosphate liquid, 0.5 mg/mL	7,250
Theophylline solution, 5.33 mg/mL	700

- PN should not be initiated if total duration of therapy is anticipated to be < 7 days.

Finally, the guideline recommends initiating supplemental PN when unable to meet 100% of targeted calorie goal after 7–10 days of EN alone (Grade E) with the notation that initiating supplemental PN prior to 7–10 days does not improve outcome and may be harmful (Grade C). This is based on the outcomes of the two meta-analyses discussed earlier.^{1,2}

The Canadian Critical Care Practice Guidelines for Nutrition in 2013 (CCPGs) present much less specific criteria warranting the initiation of PN. It recommends against any PN initiation until all means of feeding enterally have been attempted (such as obtaining small bowel feeding access and use of prokinetics). It recommends against early PN in patients at low nutrition risk or with anticipated short ICU stays. Otherwise, it states insufficient evidence to indicate a time frame for PN initiation and recommends the care provider evaluate the cost versus benefit of therapy on a case-by-case basis.²¹

In terms of maximizing the benefit of PN for patients receiving this therapy, a few items are recommended or considered by both the SCCM/ASPEN guideline and the 2013 CCPGs:

- Omit soy-based lipids
- Utilize parenteral glutamine in critical care

The SCCM/ASPEN guideline gives a Grade D recommendation for omitting soy-based lipids during the first week of ICU admission. The 2013 CCPGs recommend considering the omission of soy-based lipids in well-nourished patients with intended PN for < 10 days, but recommends care provider discretion on a case-by-case basis for malnourished patients. Avoidance of soy-based lipids would allow one to avoid the inflammatory effects of omega-6 lipids; however, it would require total avoidance of IV lipids in the United States because soy-based lipids are the only form available and meeting FDA approval. One should also consider whether the benefit of omitting IV lipid could be limited in patients receiving propofol for sedation (presently a 10% soy-based lipid solution).

Parenteral glutamine has been shown to decrease infectious complications, length of ICU stay, and mortality in the critically ill. Thus, the SCCM/ASPEN guideline gives a Grade C recommendation for its use in conjunction with PN. The 2013 CCPGs downgrade from strongly recommending IV glutamine to “should be considered” in critically ill patients receiving PN. However, it strongly recommended IV glutamine not be used in cases of shock and multiorgan failure, noting that although the REDOXS study should be excluded from this recommendation due to its combined usage of enteral and parenteral glutamine, the results could not be fully ignored.^{1,2,21} The REDOXS study was a large, multicenter study of adult ICU patients with multiorgan failure and mechanical ventilation. Patients were randomized to receive glutamine, glutamine and antioxidants, or antioxidants beginning on day 1. Patients receiving glutamine received 0.35g/kg IBW of IV glutamine daily in addition to 30 g enteral glutamine/day. Those receiving glutamine, or glutamine and antioxidants, had significantly higher 28-day and 6-month mortality, but no change in rates of organ failure or infectious complications. The 2014 REDOXS post-hoc analysis re-evaluated the initial study results while controlling for baseline covariates to determine subgroup effects. The results were largely unchanged, with the exception of greatest harm being noted in patients receiving combined glutamine and antioxidant with multiorgan failure that included baseline renal dysfunction at enrollment.^{39,40} It should be noted that the dipeptide IV glutamine that the preceding research is primarily based on is not commercially available in the United States or FDA approved. L-Glutamine is the only parenteral source in the United States, with limited availability due to stability issues.

Adjunctive Therapy

Probiotics have been shown to improve outcome by decreasing infection in critically ill patients.^{1,2,21}

Antioxidant vitamins and minerals should be given to critically ill patients requiring specialized nutrition therapy (a combination of vitamins C and E; trace elements zinc, copper, and specifically selenium) particularly in burns, trauma, and mechanical ventilation. This is the result of a meta-analysis showing significant reduction in mortality when utilized.^{1,2,21,41} Parenteral selenium was found to decrease mortality in sepsis and septic shock.^{1,2,42,43}

The SCCM/ASPEN guideline recommends enteral glutamine supplementation in burns, trauma, and mixed ICU patients when not already provided in the EN formula, with the rationale that enteral glutamine has been shown to decrease ICU and hospital length of stay in burn and mixed ICU patients and decrease mortality in burn patients. It recommends 0.3–0.5 g/kg/d glutamine given in two to three divided doses per day (Grade B).^{1,2,44–46} The 2013 CCPGs recommends only that supplemental enteral glutamine be considered in burn and trauma patients, without specific dosing recommendations. It strongly recommends that high-dose combined parenteral and enteral glutamine not be used patients with shock or multiorgan failure.²¹

Optimizing glucose control is important for minimizing mortality. Earlier stringent glucose control goals of 80–110 mg/dL have shown increased incidence of hypoglycemia. A more liberal goal of ≤ 180 mg/dL decreases mortality.^{47,48}

GUIDELINES FOR SPECIFIC DISEASE STATES

The use of high-fat, low-carbohydrate formulas for the purpose of altering RQ and reducing CO₂ production in acute respiratory failure is not recommended. Presently, there is no consensus regarding route, source, and amount of fat to provide. Existing evidence shows that the fat-to-carbohydrate ratio may only be of significance in the setting of overfeeding.^{1,2}

Standard ICU goals for calorie and protein should be utilized in the face of acute renal failure and standard enteral formulations also utilized. If there are significant electrolyte abnormalities, an electrolyte-restricted specialty formula designed for renal failure can be utilized. Acute renal failure rarely exists in an ICU setting as isolated organ failure, and the overall diagnoses and status of the patient should be considered when assessing macronutrient needs. Diets containing < 1 g/kg/day of protein have been shown to increase lean tissue loss in the ICU. Patients receiving HD or continuous renal replacement therapy (CRRT) may require up to 2.5 g/kg/d of protein to achieve positive nitrogen balance.^{1,2,49}

Traditional markers of assessing nutrition status in critically ill patients with cirrhosis or liver failure should be utilized with caution. Complications of ascites, intravascular dryness, and overall liver synthesis of visceral proteins affect weight-based estimations of needs and laboratory values. Indirect calorimetry is ideal for determining energy needs. EN is the preferred route of nutrition in acute or chronic liver disease due to decreased rates of infection and metabolic complications as

compared with PN. Protein restriction should be avoided, and protein should be provided in amounts similar to the general ICU population. Specialty enteral formulas (containing branched-chain amino acids) should be reserved for encephalopathic patients unresponsive to luminal antibiotics and lactulose.^{1,2,50}

Patients with severe acute pancreatitis (as defined by Atlanta Classification, Acute Physiology and Chronic Health Evaluation, or Ranson criteria) should have a nasoenteric feeding tube placed and EN initiated as soon as volume resuscitation is complete. Three meta-analyses reveal improved outcomes with early EN and reduction in the following when compared with PN: infectious morbidity, hospital length of stay, need for surgical intervention, multiple organ failure, and mortality.^{1,2,51,52} Patients may be fed via gastric or postpyloric access.^{1,2,53} The SCCM/ASPEN guideline gives the following recommendations to enhance tolerance of EN:

- Provide early EN to minimize the duration of ileus (Grade D).
- Position EN infusion more distally in the GI tract (Grade C).
- Change from intact EN formulation to small-peptide and medium-chain triglyceride or nearly fat-free elemental formula (Grade E).
- Switch from bolus to continuous infusion (Grade C).^{1,2}

The relative ease of achieving nasal gastric feeding access, as compared with postpyloric, can aid the delivery of early EN and improve the likelihood of EN tolerance. Although evidence does show overall tolerance of gastric feeding in severe acute pancreatitis, pancreatic exocrine stimulation is more likely with proximal feeds (as compared with feeding ≥ 40 cm below the ligament of Treitz that causes little to no stimulation). A small randomized trial demonstrated decreased bicarbonate, volume, and enzyme output production from the pancreas when jejunal bolus feedings were transitioned to continuous infusion, but it is unknown whether the same benefits would occur with gastric EN.

Last, patients with severe acute pancreatitis should be considered for PN therapy (Grade C) only after the first 5 days of hospital admission when EN is not feasible (Grade E). This is based on a study showing significant reductions in overall length of hospital stay, overall complications, and mortality when PN is delayed until 24–48 hours after full liquid resuscitation, and the latter recommendation was based on the expert opinion of the panel.^{1,2,54}

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Therapeutic Hypothermia Targeted Temperature Management: History, Data, Translation, and Emergency Department Application

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INTRODUCTION

Targeted temperature management (TTM), also known as therapeutic hypothermia (TH), has become standard of care for the management of comatose patients with return of spontaneous circulation (ROSC) after cardiac arrest. The 2010 American Heart Association (AHA) guidelines for management of post-cardiac arrest patients recommend that comatose (i.e., lack of meaningful response to verbal commands) adult patients with ROSC after out-of-hospital ventricular fibrillation (VF) cardiac arrest should be cooled to 32°C to 34°C (89.6°F to 93.2°F) for 12 to 24 hours (Class I, LOE B). Induced hypothermia also may be considered for comatose adult patients with ROSC after in-hospital cardiac arrest of any initial rhythm or after out-of-hospital cardiac arrest with an initial rhythm of pulseless electric activity or asystole (Class IIb, LOE B).¹

Very few recommendations in the AHA guidelines are assigned a Class I recommendation, and, as practitioners at the portal of entry for the majority of cardiac arrest patients,

emergency physicians (EPs) need to be familiar with this therapy, understand the rationale for the level of recommendation assigned to TTM, be capable of rapidly identifying appropriate candidates, and have the skills to initiate the therapy.

Why is TTM needed to improve outcomes after cardiac arrest? When a person suffers a cardiac arrest, no effective cardiac contractility occurs, resulting in global hypoperfusion and ischemia. Chest compressions provide some degree of circulation during arrest and high-quality chest compressions can deliver up to 40% of the cardiac output produced by a spontaneously beating heart. The ischemia that occurs during cardiac arrest triggers a number of pathologic processes including the production of reactive oxygen species, initiation of a profound inflammatory cascade, development of metabolic acidosis with accompanying elevated lactate levels, and endothelial and mitochondrial dysfunction, to name some of the dozens of derangements that ensue. When ROSC occurs, ischemic tissues are reperfused with blood, and this reperfusion produces its own injury patterns. Early reperfusion injury occurs immediately

after ROSC and lasts for approximately 30 minutes; delayed reperfusion injury begins a few hours later and continues for days.² The combination of ischemia and reperfusion produces the post–cardiac arrest syndrome (PCAS), a unique disease state requiring specialized care. This was first described by Negovsky in 1972, when he stated that postresuscitation syndrome was a unique disease entity with unique pathophysiology that needed to be understood if it was to be treated appropriately.³ Currently, TTM is the best-studied and most effective therapy for treating patients with PCAS.⁴ In this chapter, we will discuss the epidemiology of cardiac arrest, the rationale for using TTM, data supporting its use, practical aspects of implementation, and future directions for the therapy.

EPIDEMIOLOGY

Although the United States has no standardized, mandatory reporting system, it is estimated that 400,000 cardiac arrests occur each year in the United States, 75% as out-of-hospital cardiac arrests (OHCA) and 25% as in-hospital arrests.⁵ Viewed from a different perspective, one arrest arrives in an ED in the United States every 2 minutes. Europe also has approximately 400,000 arrests per year.⁶ In Japan, where a universal cardiac arrest reporting system exists, more accurate numbers are available; in 2007, approximately 78,000 OHCA occurred nationwide.⁷ Survival from cardiac arrest is abysmal—approximately 7% of OHCA in the United States survive to hospital discharge.⁵ However, survival varies significantly depending on prehospital, intra-arrest, and postarrest variables including initial arrest rhythm, whether the arrest was witnessed by a bystander, whether bystander cardiopulmonary resuscitation (CPR) was performed, ambulance response times, availability of automated external defibrillators (AED), and quality of postarrest care. Furthermore, reported survival rates are also impacted by patient inclusion criteria including EMS transport policies. Some EMS systems have robust field termination of resuscitation algorithms that limit comparison interpretation. In the United States, survival rates vary from 0.2% in Detroit to 8.3% in the greater Seattle area.^{8,9} One of the main variables affecting outcome is delivery of quality postarrest care, centered on TTM. The need for high-quality postarrest care was emphasized in a 2003 publication from the National Registry of Cardiopulmonary Resuscitation (NRCPR), a registry of in-hospital cardiac arrests. Reporting on 14,792 arrests, ROSC was achieved in 39% of the patients, who had a subsequent mortality rate of 68%, and an average time to withdrawal of care of only 1.5 days.¹⁰

HISTORY

Physicians have been interested in using induced hypothermia for clinical purposes for millennia. Hippocrates wrote about packing injured patients in ice and questioned whether this simple technique could improve outcomes. In 1814, Baron Larrey, Napoleon's chief battlefield surgeon, made observations on the effect of cold on injured soldiers. While Napoleon's army retreated from Moscow after the Russian

campaign, a policy of placing injured officers near the fire while keeping injured foot soldiers in the cold was enforced. Larrey noted that injured foot soldiers appeared to do better with similar injuries than the injured officers and commented, "Cold acts on living parts such that they may remain in a state of asphyxia without losing their lives." This statement summarizes early ideas of the mechanism of action of induced hypothermia: lowering temperature lowered metabolism, decreasing oxygen and glucose consumption and allowing injured cells time to recover.

Temple Fay, a neurosurgeon at Temple University Hospital in Philadelphia, Pennsylvania, was the first to publish studies of the clinical application of induced hypothermia. In 1940, he reported treating cancer patients with TH.^{11,12} In 1959, in the journal *Anesthesia and Analgesia*, Benson et al. from Johns Hopkins University Hospital in Baltimore, Maryland, published results of a case series of 27 perioperative cardiac arrests, some of which were treated with TH.¹³ The stated rationale for using TH was similar to that observed by Baron Larrey almost 150 years earlier: "Hypothermia has been shown to protect the brain against anoxia. There is a reduction in the cerebral oxygen consumption and cerebral blood flow with body cooling." Nineteen of the arrests were resuscitated with sustained ROSC. Twelve of the 19 were treated with TH. Fifty percent (6/12) of the patients treated with TH survived, all neurologically intact, whereas only 14% (1/7) of the patients who were not cooled survived. They concluded that "The improvement in survival rate from 14% to 50% with use of hypothermia is clinically significant and warrants the use of cooling in all patients who have had cardiac arrest with demonstrable neurological injury."¹³

In 1964, in an article published in the *Journal of the Iowa Medical Society*, Peter Safar advocated treating postarrest patients with a comprehensive management strategy centered on induced hypothermia, which included attempts to gauge the cause of arrest, support ventilations and circulation, prevent seizures, and monitor closely.¹⁴ He recommended early institution of hypothermia, stating, "start within 30 minutes if [there are] no signs of CNS recovery." There are no published case reports documenting the clinical experience of Safar and colleagues with TH at the University of Pittsburgh in the 1960s. It is generally believed that they cooled patients to 30°C using ice packs and treated post–cardiac arrest patients as well as patients with other causes of brain injury including traumatic brain injury, ischemic stroke, hepatic encephalopathy, and comatose meningitis. After treating a number of patients, they abandoned the clinical use of TH and began to study its application more closely in animal models of cardiac arrest. Reasons cited for stopping clinical application of TH included coagulopathy, arrhythmias, and hypotension. These potential side effects of TH will be addressed later in this chapter.

PILOT STUDIES

Insights from animal experiments including the potential efficacy of hypothermia performed at 33°C instead of lower

temperatures, the complexity of ischemia–reperfusion injury, the multiple physiologic processes affected by hypothermia, the need for adequate mean arterial pressure (MAP) to maintain cerebral perfusion, and a focus on patients who remained comatose after ROSC from OHCA led to reinvestigation of the utility of employing TH in humans.^{15–17} The first prospective study of TH in humans was published in the *Annals of Emergency Medicine* in 1997, by Stephen Bernard and colleagues from Australia.¹⁸ The objective of this pilot study was to investigate the effect of induced hypothermia to 33°C begun in the ED and continued for 12 hours in the ED and ICU on outcomes in patients with anoxic brain injury after OHCA. Twenty-two comatose OHCA VF patients treated with TH to 33°C for 12 hours were compared with 22 matched historic controls obtained from chart review. Primary endpoints were survival and good neurologic outcomes. Survival was 23% in historic controls versus 55% in patients treated with hypothermia ($P < .05$), and good neurologic outcomes occurred in 14% versus 50%, respectively ($P < .05$).¹⁸

In 2000, in the *Journal of the American College of Cardiology*, Nagao et al. from Tokyo, Japan, published their results treating comatose survivors of cardiac arrest with TH with or without emergency cardiopulmonary bypass (ECPB).¹⁹ They studied a convenience sample of 50 patients with an initial rhythm of VF presenting to the ED in ongoing cardiac arrest. Initially, all patients received standard CPR. If ROSC was achieved and systolic blood pressure (SBP) could be maintained above 90 mm Hg, then hypothermia was induced. If ROSC was not achieved, patients were placed on ECPB as a rescue strategy, followed by treatment with TH if blood pressure was adequate. Of the 23 patients treated with TH, 12 (53%) had good neurologic outcomes. These pilot studies led investigators to pursue true, randomized controlled trials of TH in comatose survivors of OHCA.

RANDOMIZED TRIALS AND LANDMARK STUDIES

In 2001, Hachimi-Idrissi et al. published a randomized trial of cooling with a helmet device to achieve a target temperature of 34°C.²⁰ Thirty patients who remained comatose after ROSC from asystole or pulseless electrical activity (PEA) cardiac arrests were randomized to either normothermia (14 patients) or hypothermia (16 patients). The study was designed to test the feasibility of inducing TH using a helmet cooling device, not the efficacy of TH in this patient population. The hypothermia patients reached target core (bladder) temperatures in a mean of 180 minutes from start of therapy. Survival was low in both arms of the study: 3/16 (18.8%) survived in the hypothermia group; 1/14 (7.1%) survived in the normothermia group. Rates of good neurologic outcome were also low: 2/16 (12.5%) patients who were cooled and none of the patients who were not cooled had good neurologic recovery.

Bernard et al. followed up their pilot study of TH with a pseudo-randomized trial of TH compared with normothermia, which was published in *The New England Journal*

of Medicine in 2002.²¹ Seventy-seven patients who remained comatose after resuscitation from OHCA caused by VF were randomly assigned to treatment with TH or normothermia depending on the day of the week. On odd-numbered days patients were treated with induced hypothermia and on even-numbered days with normothermia. Hypothermia therapy was begun by paramedics in the field who removed the patient's clothing and applied cold packs. The target temperature was 33°C, and hypothermia was maintained for 12 hours. The target temperature was 37°C in the normothermia group who were treated with sedatives and paralytics to prevent shivering. The primary outcome measure was survival to hospital discharge with good neurologic function. Twenty-six percent (9/34) of patients treated with normothermia had good neurologic outcomes versus 49% (21/43) of patients treated with hypothermia ($P = .046$). When adjusted for potential confounders including age and time to ROSC, the survival benefit with good neurologic outcome associated with TH remained (OR = 5.25; 95% confidence interval [CI] 1.47–18.76; $P = .011$; see Figure 59-1).

In the same issue of *The New England Journal of Medicine*, the Hypothermia After Cardiac Arrest (HACA) Study Group published the results of a larger, randomized, prospective trial comparing hypothermia to normothermia in patients who remained comatose after being resuscitated from OHCA caused by VF.²² The target temperature range was 32–34°C for 24 hours. The primary outcome measure was good neurologic outcome at 6 months. Secondary endpoints included mortality at 6 months and the rate of complications during the first 7 days. Good outcomes occurred in 55% (75/136) of the TH patients versus 39% (54/137) of the normothermia patients (RR = 1.40; 95% CI 1.08–1.81). Mortality was reduced from 55% in the normothermia group to 41% in the TH group, which was statistically significant. Despite

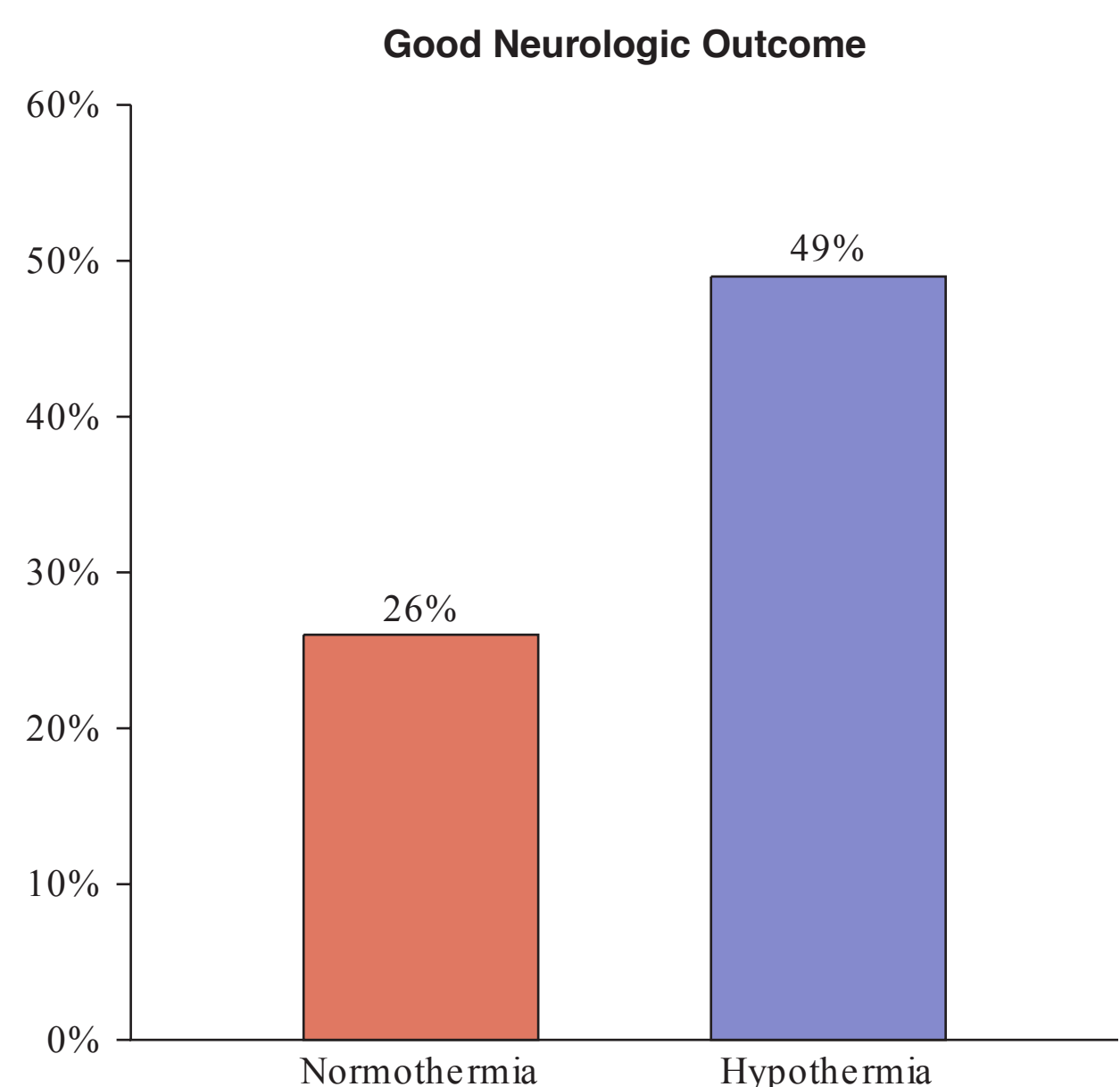


FIGURE 59-1 Bernard trial outcomes.

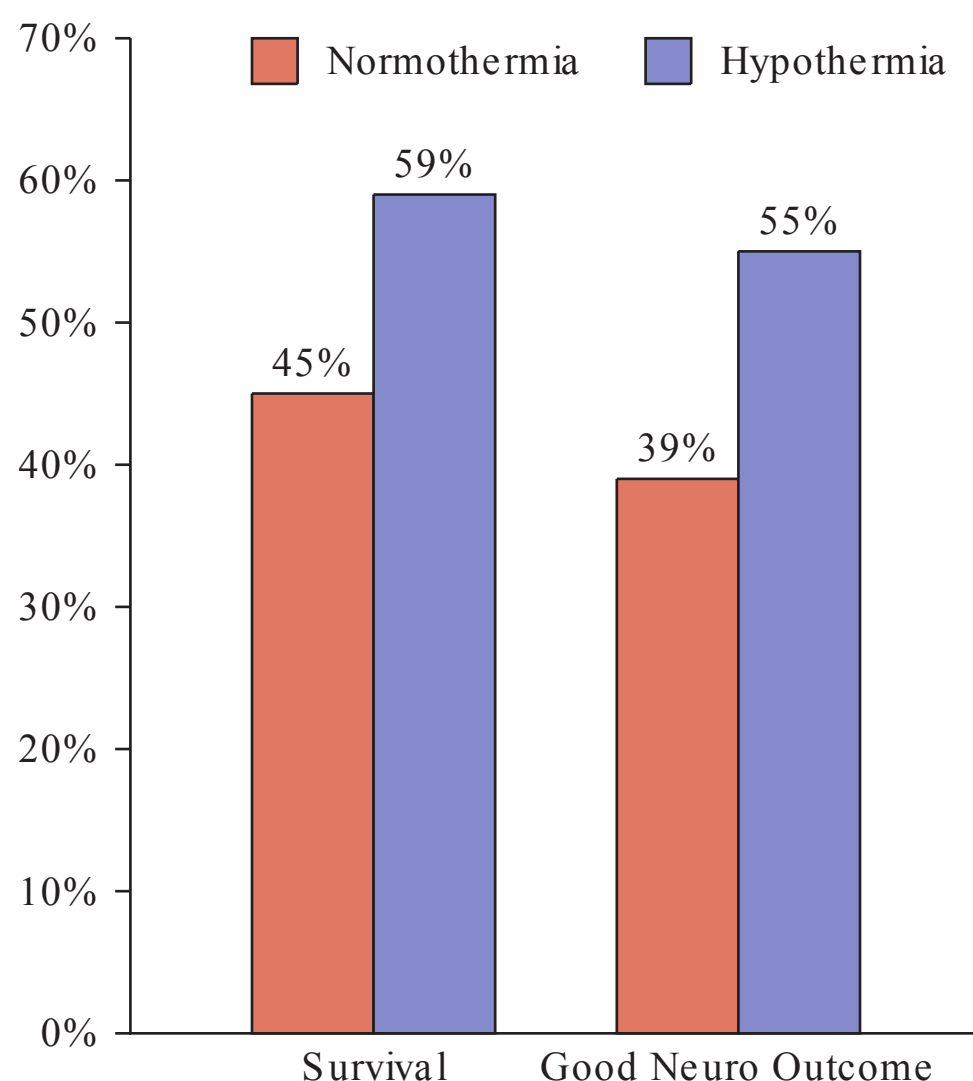


FIGURE 59-2 HACA trial outcomes.

concerns of infection, bleeding, and dysrhythmias, there were no statistically significant differences in the rate of complications between the two groups (see Figure 59-2). Notably, the median temperature in the normothermic group was 37.8°C, suggesting that a significant portion of control patients were actually febrile.

CALL FOR ADOPTION OF THERAPEUTIC HYPOTHERMIA

In 2003, the International Liaison Committee on Resuscitation evaluated the results of these randomized trials and concluded that TH should be used to treat comatose patients resuscitated from OHCA caused by VF.²³ In 2005, the AHA guidelines for postresuscitation support recommended that “unconscious adult patients with ROSC after out-of-hospital cardiac arrest should be cooled to 32°C to 34°C (89.6°F to 93.2°F) for 12 to 24 hours when the initial rhythm was VF (Class IIa). Similar therapy may be beneficial for patients with non-VF arrest out of hospital or for in-hospital arrest (Class IIb).”²⁴ The central question accompanying these recommendations is the following: When TH is applied in a heterogeneous group of health care settings, will the benefit observed for the therapy in the randomized trials be maintained?

DATA FROM IMPLEMENTATION STUDIES AND DATABASES

Multiple implementation studies have been published since the randomized controlled trials of TTM were published in 2002.^{25–30} These implementation studies have had varying inclusion criteria including differences in age, the presence of a witness, the presenting rhythm, and duration of downtime. They have used different cooling techniques and maintained hypothermia for varying lengths of time. These diverse

implementation studies were summarized in a meta-analysis published by Sagalyn et al. in *Critical Care Medicine* in 2009.³¹ They examined all nonrandomized studies of adults resuscitated from cardiac arrest, with or without historic controls, published after the Bernard and HACA studies were in print in early 2002. Thirteen studies were included in the analysis, with a total of 924 TH patients and 336 normothermic, historic controls. The meta-analysis concluded: “The survival and neurological outcomes benefit from therapeutic hypothermia are robust when compared over a wide range of studies of actual implementation.” The odds ratio for survival when treated with TH was 2.5 (95% CI 1.8–3.3) and for favorable neurologic outcome was also 2.5 (95% CI 1.9–3.4).³¹

Two large multi-institutional databases have also been published. The first, published by Arrich and the European Resuscitation Council Hypothermia After Cardiac Arrest Registry Study Group in 2007, was an outgrowth of the HACA trial. A total of 587 patients were included, 462 of whom were treated with TH and 123 with normothermia.³² Survival was 57% in patients treated with TH versus 32% in normothermic patients ($P < .001$); favorable neurologic outcomes were achieved in 45% of TH patients versus 32% of normothermic patients ($P = .02$). The second, from Nielsen et al., summarized 4 years of data from cases entered into the “Hypothermia Network,” a 34-center, 7-country registry of OHCA patients who remained comatose after resuscitation and were treated with TH.³³ Nine hundred and eighty-six patients were included; the median time from collapse to ROSC was 20 minutes (IQR 14–30), the median time from collapse to initiation of TH was 90 minutes (IQR 60–165), and the median time from collapse to target temperature was 260 minutes (IQR 178–400). The presenting rhythm was VF/VT in 686 patients, of whom 412 (61%) survived to 6-month follow-up and 380 (56%) had good neurologic outcomes. Of the 217 patients who presented with asystole, 54 (25%) survived to 6 months and 46 (21%) had good outcomes. For the 66 patients presenting with PEA, 18 (27%) survived to 6 months and 15 (23%) had good outcomes. These robust database results lend support to the efficacy of TH when applied to diverse patients in varying clinical settings with a wide range of resources.

BUNDLES OF POSTARREST CARE

These nonrandomized results provide strong, ancillary support to the findings of the randomized trials and suggest that TH should be used to treat the majority of comatose survivors of cardiac arrest regardless of initial rhythm or location of arrest. The totality of the findings from the randomized trials, implementation studies, and databases has informed the changes in the 2010 AHA recommendations about post-cardiac arrest care.¹ As the authors acknowledged in the introduction: “There is increasing recognition that systematic post-cardiac arrest care after . . . ROSC can improve the likelihood of patient survival with good quality of life.”¹ They recommend that TH be combined with other interventions to optimize outcomes in PCAS patients. These other interventions include optimization

of cardiopulmonary function and vital organ perfusion, early percutaneous coronary intervention, goal-directed critical care, and neurologic support.

THE TTM TRIAL: REFINING POST-CARDIAC ARREST CARE

Lingering concerns about the strength of data from the Bernard and HACA trials led to interest in performing additional randomized trials testing the efficacy of TTM. The central concerns included (1) the control group in the HACA trial had a mean temperature of 37.8°C and in the Bernard trial of 37.4°C, and the control group temperatures were not strictly regulated; (2) the trials only included patients with an initial shockable rhythm, and this limited translation to comatose patients with nonshockable rhythms; and (3) neither trial included a strict protocol for neuroprognostication and withdrawal of care.^{21,22} To address these concerns, Niklas Nielsen, Hans Friberg, and colleagues designed the TTM trial. In the trial, 950 unconscious adults after OHCA of presumed cardiac etiology were randomized at 36 hospitals throughout Europe and Australia over a 27-month period to a target temperature of either 33°C or 36°C.³⁴ The mean time to randomization for enrolled patients was 2 hours.

This was a highly selected patient population: 80% had a shockable initial rhythm, 89% were bystander witnessed cardiac arrests, 73% had bystander CPR, and the median time to initiation of basic life support was 1 minute (IQR 0–2 min). Median times to start of ALS was 10 minutes and to ROSC was 25 minutes (IQR 17–40 min). There were no significant differences in these factors between the 33°C and 36°C groups.

Both groups received precise temperature management with an intervention period of 36 hours, which began at the time of randomization. The investigators followed a strict protocol, attempting to achieve the assigned temperature as quickly as possible. At hour 28, gradual rewarming to 37°C was commenced with rewarming proceeding at 0.5°C/hr. In addition, the participating sites were encouraged to maintain patient temperature below 37.5°C, using their specific institutional protocols, until 72 hours after arrest. Finally, there was a strict neuroprognostication algorithm to prevent early withdrawal of care, which delayed neuroprognostication until at least 108 hours of intensive care were performed in the majority of patients.

The primary outcome measure was all-cause mortality through the end of the trial. Secondary outcomes included the composite endpoint of poor neurologic function or death at 180 days. Death occurred in 50% (237/473) of the 33°C patients versus 48% (225/466) of the 36°C patients (hazard ratio with 33°C = 1.06; 95% CI 0.89–1.28; $P = 0.51$). At 180 days, the secondary outcome composite endpoint was seen in 54% of the 33°C group versus 52% of the 36°C group. There were no statistically significant differences in the rate of complications including infection, bleeding, arrhythmias, or electrolyte and metabolic disorder except hypokalemia (19%

of the 33°C group versus 13% of the 36°C group; $P = 0.018$). An analysis of six predefined subgroups including age, gender, time from arrest to ROSC, initial rhythm, presence of shock at admission, and number of patients enrolled per site found no statistically significant differences between 33°C and 36°C.

THE CHANGING LANDSCAPE AFTER THE TTM TRIAL

This well-done trial has produced a lot of discussion about whether the target temperature should remain at 33°C, should be raised to 36°C, or if a more flexible target should be pursued. Although the data are compelling, how generalizable they are is unclear. The low flow/no flow time of this predominantly shockable cohort may not reflect the general patient population cared for in many EDs. The existing data are not definitive to conclude superiority of any one target temperature. Unfortunately, the trial has also been misinterpreted to suggest that TTM doesn't work and is unnecessary. Both arms of the trial are active temperature management. Target temperature should be guided by local, institutional consensus. Further research is needed to investigate whether patients with varying degrees of neurologic and cardiac dysfunction shortly after ROSC may benefit from different TTM strategies. Various strategies may include tailoring induction strategies, duration of temperature management, depth of temperature management, and incorporating point of care, multimodal neuroprognostication tools to determine need for continued TTM.

DETAILS OF THERAPEUTIC HYPOTHERMIA

Hypothermia therapy can be divided into three distinct phases: induction, maintenance, and rewarming.³⁵ *Induction* involves bringing the patient from the presenting temperature to target temperature. This can be accomplished by a number of methods: infusion of chilled intravenous fluids, application of ice bags, application of surface cooling equipment, insertion of intravascular cooling catheters, and other, novel equipment. In the Hypothermia Network Registry, the most common methods used to induce hypothermia were chilled fluids, used in 80% of the patients, and ice bags, used in 43% (see Figure 59-3).³³ Induction should begin as close to ROSC as possible and occur at as fast a rate as possible. Shivering is the major complication that can occur during induction of TTM and can be controlled with a number of different agents including meperidine, magnesium, buspirone, or paralytics. Benzodiazepines and neuromuscular blocking agents were used in all of the patients in the Bernard and HACA trials to control shivering and induce sedation. In the TTM trial, all sites were required to use a sedation protocol, although specifics were not mandated in the study protocol. In addition, as the patient's core temperature drops, metabolism slows (decreasing approximately 8%/1°C), oxygen and

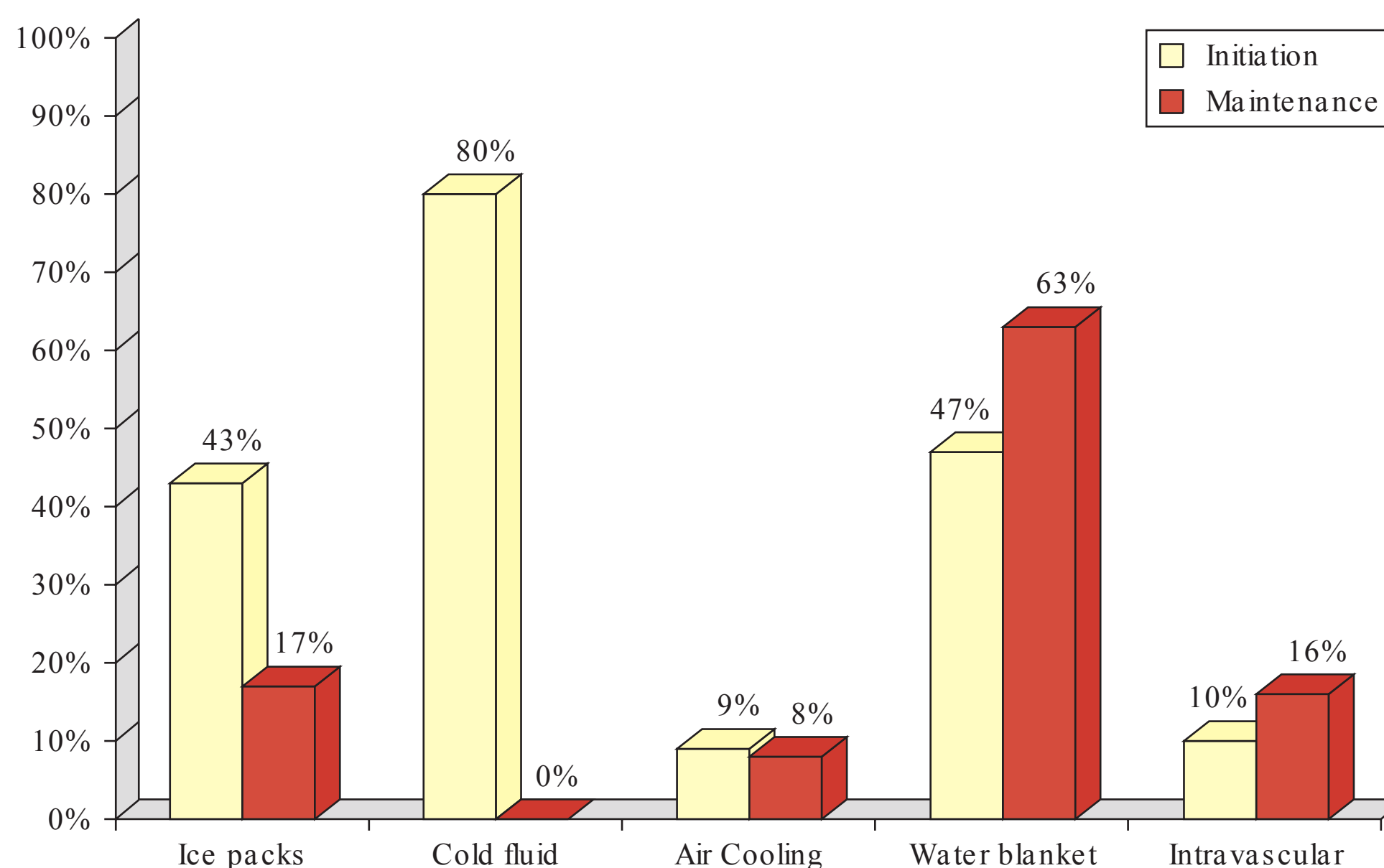


FIGURE 59-3 Methods of cooling from Nielsen study.

glucose consumption fall, and ventilator settings need to be adjusted to compensate for decreased carbon dioxide production.³⁵ Continuous core temperature measurement should be established during the induction phase. Placement of an esophageal or urinary bladder probe should be considered, particularly if using a device that allows temperature auto-regulation via a feedback loop.

During the *maintenance phase*, patients are kept at the target temperature for a specified period of time. The optimal length of time to maintain hypothermia is unknown. In the Bernard trial, target temperature was maintained for 12 hours; in the HACA and TTM trials 24 hours; in the Hypothermia Network Registry, 93% of the patients received TH for 24 hours.^{21,22} The period of injury after ischemia and reperfusion may last up to 7 days, and longer periods of TTM may produce better outcomes.³⁵ In the maintenance phase, several clinical problems need to be addressed: many patients develop postarrest myocardial stunning with accompanying decrease in ejection fraction; TTM causes a cold-induced diuresis, and many patients require additional volume infusion to maintain adequate intravascular volume; and electrolyte changes include hypokalemia, hypomagnesemia, and hyperglycemia.³⁵

The goal of the *rewarming phase* is to safely return the patient to normothermia in a controlled fashion. This can be facilitated by using a cooling device with a feedback mechanism and an automatic rewarming program. During the rewarming phase, the patient begins to vasodilate, potentially causing a relative hypovolemia requiring infusion of additional intravenous fluid. Potassium moves from intracellular compartments to the intravascular compartment, and patients can become hyperkalemic; similarly, insulin resistance decreases and patients on continuous insulin infusions

can become hypoglycemic. Ventilator settings need to be changed to account for the increased carbon dioxide production as metabolism increases.³⁵

EMERGENCY DEPARTMENT–SPECIFIC CONCERNS

The role EPs play in the management of PCAS patients varies from institution to institution, depending on hospital resources, patient flow, and ED capabilities. Many OHCA patients have ROSC prior to ED arrival; others receive CPR in the ED, and a percentage of them attain ROSC while in the ED. EPs can maximize ROSC by delivering high-quality CPR including early defibrillation,³⁶ quality chest compressions,³⁷ and discovery and treatment of reversible causes.³⁸ Rapid identification of patients who qualify for TTM and other aspects of postarrest care is a central task of EPs.^{14,21,22} In addition to assessing for persistent coma after ROSC, this may involve—as dictated by the clinical scenario—obtaining basic labs to evaluate coagulation function and brain imaging to ensure no intracranial hemorrhage. In addition, in the vast majority of cases, induction of TTM in patients who remain comatose after resuscitation from OHCA will fall under the auspices of EPs. This may be as simple as identification of qualifying patients, placement of a core temperature monitoring device, application of ice bags, infusion of chilled saline through peripheral IVs, and rapid transfer to an ICU for definitive management. On the other hand, it may include the first hours of comprehensive postarrest care including induction of TTM, placement of arterial and central venous catheters, hemodynamic optimization, initiation of neurologic monitoring, ventilator management, electrolyte management, and bedside echocardiography. Comprehensive PCAS

management programs need to be developed with champions from EMS, the ED, cardiology, critical care, neurology, and, potentially, rehabilitation medicine that protocolize care and determine target temperature.^{4,30} It is imperative to delineate the responsibilities of each group of providers, given the potential rapid transition of these critically ill patients and number of interventions that need to be performed in the proximal phase.

FUTURE DIRECTIONS

The number of PCAS patients qualifying for TTM and other aspects of postarrest care who present to different hospitals around the country varies from a few a year to several a month. Studies have demonstrated that outcomes from cardiac arrest vary depending on hospital type, with lower survival rates at more rural, nonteaching, and smaller hospitals than at urban, teaching, and larger hospitals.^{39,40} Therefore, postarrest care may be optimized if regionalization occurs by diverting patients from low-volume hospitals to those treating a larger number of PCAS patients. In Arizona, the state EMS system has instituted a program of comprehensive cardiocerebral resuscitation, including TTM delivered at cardiac arrest receiving hospitals. Using this approach, they have increased survival from 3.8% to 9.1%.³⁸

When a cardiac arrest patient does not have ROSC, there are limited options available to the physicians attempting to resuscitate the patient. After a period of unsuccessful resuscitation, the EP can halt further resuscitation efforts and pronounce the patient dead. The only alternatives available at this time are continued CPR by conventional means including chest compressions, drug administration, and defibrillation, or placing a patient on ECPB to provide circulation and ventilation for the patient until heart function recovers. During the time the patient is on ECPB, reversible causes of arrest can be addressed. Feasibility studies from Tokyo, Taipei, Seoul, and Los Angeles have demonstrated promising outcomes using ECPB; however, no randomized, prospective studies have been conducted, and survivors may reflect selection bias, a Hawthorne effect, or an epiphenomenon of the timing of the intervention.

2010 AHA Recommendations for Therapeutic Hypothermia	
Rhythm	Recommendation
Out-of-Hospital Ventricular Fibrillation	Class I, Level of Evidence B
In-Hospital Arrest	Class IIb, Level of Evidence B
Pulseless Electrical Activity, Asystole	Class IIb, Level of Evidence B

FIGURE 59-4 2010 American Heart Association recommendations for therapeutic hypothermia.

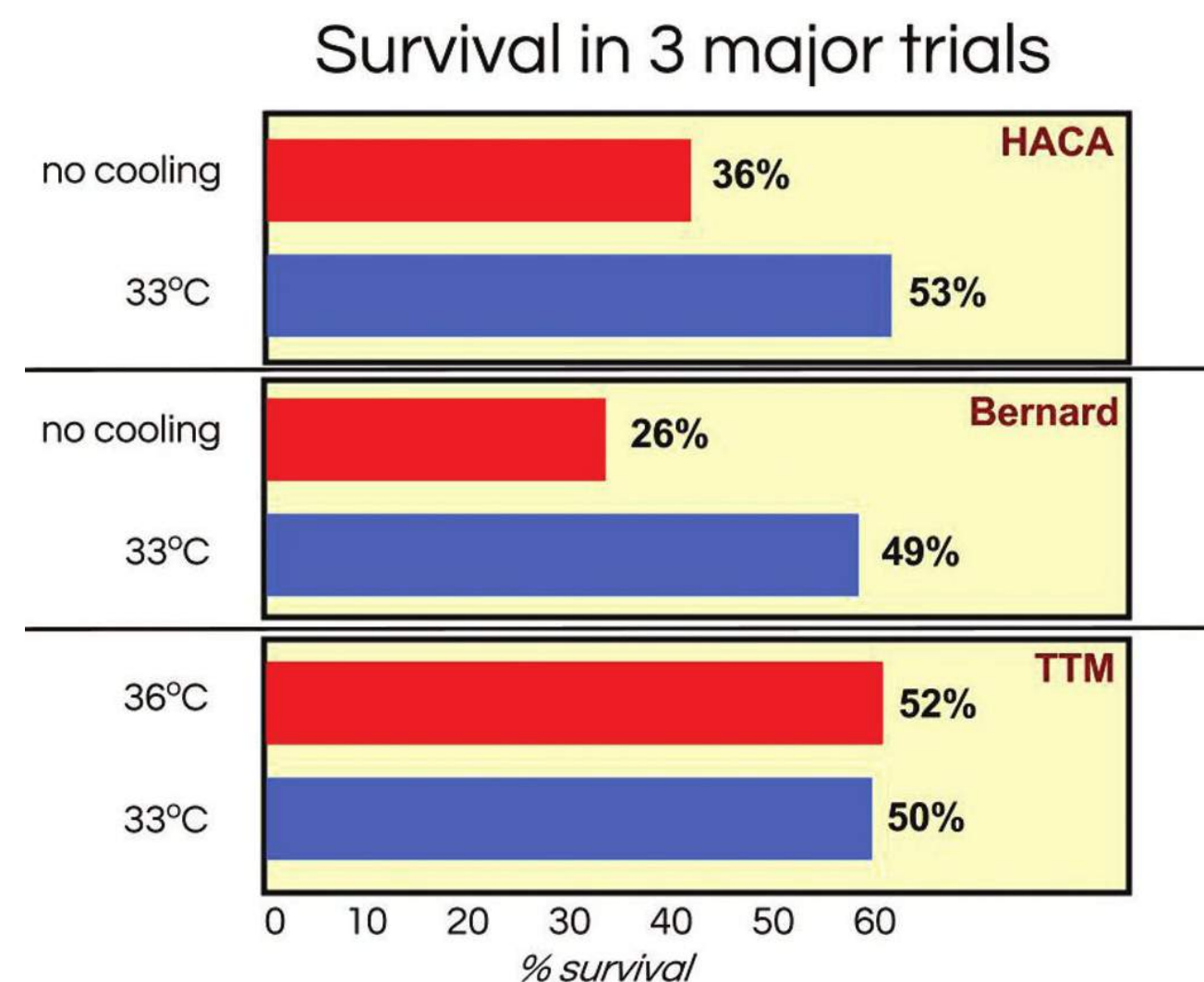


FIGURE 59-5 Comparison of outcomes in Bernard, HACA, and TTM studies. (Used with permission from Ben Abella, MD.)

CONCLUSION

TTM is the standard of care for patients who remain comatose after resuscitation from cardiac arrest (see Figure 59-4). The current data suggest that 36°C is as effective as 33°C as a target temperature. An organized program of TTM needs to be integrated into a comprehensive plan for management of PCAS patients. EPs must develop these programs in concert with colleagues from EMS, neurology, cardiology, intensive care, and rehabilitation medicine. Clear delineation of who will be cooled, how they will be cooled, and the division of labor among the different care providers is vital to ensure a successful TTM program.

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The Multisystem Trauma Patient

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Critically ill patients with traumatic injuries are often complex, encompassing a wide array of problems. Their care often starts before they arrive at the hospital, continues from the time they arrive in the emergency room, and will likely consist of days in the hospital with rehabilitation after. A series of specialists is often required, including emergency medicine, trauma surgery, orthopedic surgery, neurosurgery, anesthesia, and facial surgery among others. This chapter will focus on the initial care of the critically ill patient with multisystem trauma in the emergency room.

PREHOSPITAL COURSE

Care of the multisystem trauma patient usually begins in the prehospital setting. Protocols are in place for emergency providers who initiate care. They are in contact with physicians at the receiving hospital to coordinate care and allow for adequate preparation of the emergency room resources and personnel. The initial management goals are to prevent further injury, initiate resuscitation, and to transport to the nearest appropriate facility, ideally a trauma center. Treatment provided includes the essential components of resuscitation including maintenance of the airway, hemorrhage control, immobilization of the cervical spine, and stabilization of fractures. In addition, prehospital personnel obtain background information including mechanism of injury, associated events, and past medical history to facilitate quicker diagnosis and treatment.¹ The quality of prehospital care has been shown to impact patient outcome.²

TRIAGE

The accurate triage of the multitrauma patient is essential to providing appropriate timely care and avoiding morbidity, mortality, and the overutilization of resources. Many trauma systems over-, under-, or mistriage patients. The impact of undertriage can be great, with delayed or even missed injuries and interventions. The overtriage of patients can lead to significant burden on the hospital and systemwide resources and personnel.³ The American College of Surgeons Committee on Trauma guidelines states that priority has been given to decrease undertriage to prevent morbidity and mortality from delayed definitive care.⁴ An undertriage rate of 5–10% is generally thought of as acceptable.⁵

The trauma resuscitation team is made up of physicians, nurses, respiratory therapists, radiographic technologists, lab technicians, and other allied health personnel. Most trauma centers have a multitiered activation system, and the severity of the injured patient—in addition to the hospital level—will determine who responds to the trauma activation. In Level I and II trauma centers, the full trauma team needs to respond within 15 minutes for the highest level of activation and within 30 minutes at Level III or IV centers. Minimum criteria for full trauma team activation include confirmed blood pressure < 90 mm Hg at any time; gunshot wounds to the neck, chest, or abdomen or extremities proximal to the elbow or knee; Glasgow Coma Scale (GCS) score of < 9 with mechanism attributed to trauma; transfer patients from other hospitals receiving blood to maintain vital signs; intubated patients from the scene or patients who have respiratory

compromise or are in need of an emergent airway; and emergency physician's discretion.⁴

The Eastern Association of Trauma has published guidelines with Level 2 evidence for both prehospital and in-hospital triage. For adult prehospital triage, they state that a combination of physiologic and anatomic parameters along with mechanism of injury (MOI), comorbidities, and demographics provides better triage than any smaller combination, and physiologic parameters are more accurate than anatomic parameters if used as a single criteria. For adult in-hospital triage, they state secondary triage with a tiered response is safe, accurate, and useful in optimizing team and resource utilization. A combination of physiologic and anatomic parameters with mechanism provides better triage than any single factor, but mechanism alone may not be useful and should not be used as stand-alone criteria for highest level trauma team response; the GCS Motor Score is valid for blunt trauma triage.⁶

HOSPITAL ARRIVAL

When the receiving hospital is notified of the multisystem trauma patient, an activation is initiated. Trauma centers typically have a tiered trauma activation based on predetermined prehospital criteria including physiologic, anatomic, and mechanism of injury criteria and comorbid conditions. The required response personnel vary depending on the level of the trauma activation. The most seriously injured patients require a full complement of personnel including a trauma surgeon, an emergency medicine physician, surgical and emergency medicine residents, emergency department nurses, a laboratory technician, a radiology technologist, a critical care nurse, an anesthesiologist or certified registered nurse anesthetist, an operating room nurse, security officers, a chaplain or social worker, and a scribe.⁴ Communication is also of utmost importance, with all personnel understanding and being able to carry out their responsibilities. In addition to the proper personnel being present, universal precautions should be followed by all members of the trauma team. Finally, all of the necessary equipment should be tested and readily available. This includes airway supplies, bedside diagnostic equipment, and any invasive devices such as central line kits or chest tube trays.

INITIAL SURVEY

The primary survey is the first assessment of the trauma patient after he or she arrives in the emergency room. The time to definitive care is crucial and has been shown to affect patient outcome. To streamline this initial assessment, a rapid sequence of steps has been developed and follows Advanced Trauma Life Support (ATLS) principles. This is a way to quickly and efficiently evaluate the patient's vital functions and to establish treatment priorities.⁷ The primary survey consists of the ABCDEs of trauma care and is used to identify life-threatening injuries. It follows a consistent and repeated sequence: A, airway maintenance with cervical spine protection; B, breath and ventilation; C, circulation with

hemorrhage control; D, disability and neurologic status; and E, exposure/environmental control (completely undress the patient, but prevent hypothermia). This information must be clearly communicated with all members of the trauma team. If a systematic approach is not followed, errors can be made by the resuscitation team and lead to potential patient harm.⁸ Any deviations in patient course require starting again at the beginning of the algorithm.

Airway

Airway management is the most important priority in caring for the trauma patient. The inability to secure an airway and failure to oxygenate and ventilate can be the difference between life and death. Hypoxia and hypoventilation have been associated with increased morbidity and mortality in trauma patients and are potentially preventable causes of death. Hypoxia contributes to secondary brain injury, and hypoventilation may increase intracerebral pressure.⁹ All patients should receive supplemental oxygen as initial therapy as the decision to establish a definitive airway is made. The airway should be assessed and kept clear of blood and secretions. A quick assessment of the oropharynx, nose, maxilla, mandible, and neck should also be performed.¹⁰ Indications for intubation in trauma patients include airway obstruction, hypoventilation, severe hypoxemia despite supplemental oxygen, severe cognitive impairment ($GCS \leq 8$), major cutaneous burn ($> 40\%$), prolonged transport time, and impending airway obstruction.¹¹ Trauma patients should have cervical spine immobilization during intubation, usually with inline stabilization. Rapid-sequence intubation utilizing an induction agent followed by a paralytic is used to achieve optimal conditions for intubation. The goal is sedation, neuromuscular blockade, and maintenance of hemodynamic stability. Common agents used for induction include midazolam, etomidate, ketamine, and propofol. A short-acting depolarizing agent such as succinylcholine may be used to minimize duration of paralysis.¹² Non-depolarizing agents may also be used, especially in patients in whom succinylcholine is contraindicated, such as those with allergy, history of malignant hyperthermia, large burns, and patients who have suffered a crush injury.¹³ Once the endotracheal tube is placed, confirmation is obtained by bilateral chest sounds and presence of end-tidal CO_2 via colorimetric change or capnographic change. A chest X-ray should also be obtained to ensure proper tube position.¹⁴ The endotracheal tube should then be secured.

For those patients with a difficult airway, a surgical airway is always an option. A cricothyroidotomy is an effective method for obtaining an airway. It is in the treatment algorithm for a difficult airway if orotracheal intubation has failed and the pharynx is occluded by blood or vomitus, if the patient is unable to be effectively oxygenated and ventilated by bag-valve mask ventilation, or if the patient has severe neck or laryngotracheal injury and severe airway obstruction.¹¹

Patients with polytrauma often have facial or laryngeal trauma that offers a unique challenge to obtaining an airway. Damage to the soft tissues, bones, tongue, and larynx can

cause edema, hemorrhage, and secretions leading to intrinsic and extrinsic compression of the airway. Patients with laryngo-tracheal trauma may exhibit hoarseness, stridor, or subcutaneous emphysema.¹⁵ Although many patients may need an emergent surgical airway, if the patient is able to clear blood and secretion, he may be able to be transported to the operating room for a fiberoptic bronchoscopy, awake tracheostomy, or orotracheal intubation in a controlled setting.

Breathing

Once the patient has an established airway, attention should be turned to breathing. This includes both oxygenation and ventilation. The patient should be connected to a pulse oximeter as a noninvasive measure of arterial blood saturation. It may be inaccurate in the setting of carbon monoxide poisoning and low perfusion states such as peripheral vasoconstriction and hypothermia.¹⁶ In these patients, an arterial blood gas should be sent. While breathing is the second step in the initial assessment, breathing problems can be life-threatening, and a patent airway does not guarantee adequate ventilation. Physical exam is very important in the assessment of breathing. The chest wall should be inspected for symmetry in chest wall motion; penetrating, open, or sucking wounds; deformities; and accessory muscle use. Auscultation of breath sounds can diagnose a hemo- or pneumothorax by differences in breath sounds or absence of breath sounds. Palpation of the chest wall can diagnose deformities, crepitus, or an unstable chest wall.

Patients with life-threatening breathing conditions need immediate intervention. A tension pneumothorax is a collapsed lung caused by air in the pleural space from the trachea, bronchi, or chest wall. Needle decompression followed by tube thoracostomy is the treatment of choice. Respiratory distress may also be caused by a massive hemothorax, which is blood in the pleural space, which also necessitates a tube thoracostomy and potential operative intervention.¹⁷

Circulation

One of the leading causes of death after blunt trauma is hemorrhage. The most important treatment in hemorrhage is to stop the bleeding. There are five major places where blood loss occurs in an adult trauma patient: the thoracic cavity, the abdominal cavity, the pelvis, long bone fractures, and external bleeding. For external bleeding, direct pressure over the bleeding vessel or a possible tourniquet or suture ligation in cases of scalp wounds can be used to stop the hemorrhage. For bleeding in the thoracic cavity, tube thoracostomy followed by operative intervention is the treatment of choice. If a patient has an intra-abdominal source of bleeding, either operative intervention with an exploratory laparotomy or angiography with embolization for a solid organ source may be necessary. Patients with bleeding pelvic fractures require pelvic stabilization followed by angiography with embolization. Long bone fractures should be placed in traction.

Patients should be placed on monitoring devices upon arrival to the trauma bay. Heart rate and blood pressure are

used to assess patient hemodynamics. In addition, skin color and temperature and mental status are also used as markers of end organ perfusion. Hypovolemia is seen in patients with a thready weak pulse, ashen and cool skin, and altered mental status. Tachycardia is also seen; however, patients taking certain medications such as β -blockers and calcium channel blockers will lose this response. Hypotension may not be seen in patients until 30% of their blood volume is lost. Also note that older patients with a higher baseline systolic blood pressure may have poorer perfusion at a systolic blood pressure of 100–110.

Hypovolemic shock is the most common cause of shock in trauma patients and is treated by identifying and stopping the bleeding. Intravenous access should be obtained, ideally with two large-bore peripheral catheters (minimum 16 gauge). If this is unable to be performed quickly, either a large-caliber central venous catheter or an intraosseous catheter may be used. The initial fluid bolus is 1 L of warmed intravenous fluids, followed by continued hemostatic resuscitation with either fluid or blood products to correct the signs and symptoms of inadequate perfusion including altered mental status, tachycardia, hypotension, and low urinary output. The aim is to maintain perfusion without over-resuscitation until the bleeding is controlled. Then the goal is definitive control of bleeding if needed.

Other types of shock that acute multiply injured trauma patients experience are cardiogenic or neurogenic. Patients with cardiac tamponade, blunt cardiac injury, or tension pneumothorax may exhibit signs of cardiogenic shock. Treatment includes pericardiocentesis for tamponade followed by operative intervention. For blunt cardiac injury, treatment includes close monitoring in the ICU and appropriate treatment for hypotension. A tension pneumothorax requires needle decompression of the pleural space followed by tube thoracostomy.

Neurogenic shock is a result of a spinal cord injury. Isolated intracranial injuries do not cause neurogenic shock. Sympathetic tone to the peripheral blood vessels can be lost in cervical or upper thoracic spinal cord injuries leading to hypotension. Patients with neurogenic shock have hypotension without tachycardia or vasoconstriction and may be bradycardic secondary to the unopposed vagal stimulation of the heart.¹⁸ These patients should be treated with fluid resuscitation and intervention of their spinal cord injury per the spine service.

Septic shock is another type of shock rarely seen immediately after traumatic injuries, but may manifest later if the patient survives past the initial insult. Penetrating abdominal injuries lead to intraperitoneal contamination and can lead to septic shock. These patients present similarly to patients with hemorrhagic shock and can be difficult to distinguish initially, but laboratory values and echocardiographs are helpful in diagnosis.

Disability

A brief neurologic assessment should be performed after the life-threatening injuries are found and treated during the

ABCs. This includes level of consciousness; eye motion and pupillary assessment of size, symmetry, and reaction to light; motor function; and degree of sensation. The GCS is an objective clinical tool to assess severity of brain injury. It takes into account eye opening, verbal response, and best motor function: a score of 13–15 indicates a minor injury, 9–12 indicates a moderate injury, whereas ≤ 8 is severe. It must also be kept in mind that patients may have an altered level of consciousness without evidence of a brain injury due to decreased cerebral perfusion from hypotension. Changes in GCS may mean increased intracranial pressure and worsening brain injury. Computed tomography of the head should be obtained for suspected intracranial trauma.¹⁹

Exposure

The final portion of the initial assessment is exposure. The patient should be undressed from head to toe and carefully examined. Care should be taken to avoid hypothermia by use of fluid warmers, increased room temperature, and external passive and active warming techniques.

TEAM APPROACH

The trauma team needs to display certain characteristics including leadership, mutual performance monitoring, backup behavior, adaptability, and appropriate team orientation in order to be effective and provide the best care possible for the patient.²⁰ There should be a team leader who is trained in ATLS, and this team leader supervises and directs the assessment. Communication is also paramount to ensure that team members know their defined roles, in addition to ensuring cooperation and high-quality task performance. It is also crucial that information attained during the assessment is transferred to all of the team members.²¹ In order to improve teamwork, performance, and efficiency of patient care in the trauma bay, structured or simulated training activities have been developed and shown to be successful.^{22–25}

ROLE OF IMAGING IN TRAUMA PATIENTS

After the primary survey is completed, the secondary survey begins. Imaging of the chest and pelvis with plain radiographs can be done quickly to identify life-threatening injuries such as a widened mediastinum and unstable pelvis fracture. The decision can then be made regarding additional imaging, which typically consists of CT scans, noncontrasted images of the head and cervical spine, and contrasted images of the chest, abdomen and pelvis in hemodynamically stable patients.²⁶ Multidetector CT (MDCT) scanners have decreased scan times while increasing image resolution due to thinner collimation and reduced partial volume and motion artifacts. These images can then be used for multiplanar reformats and three-dimensional visualization of the thoracic and abdominal aorta, cervical and thoracolumbar spines, maxillofacial skeleton, and pelvis and acetabulum.^{26,27}

Head Imaging

Imaging of the head should be performed if there is concern over a suspected brain injury. This includes objective injury to the brain such as decreased level of consciousness, facial or cranial deformity, leakage of CSF, hemotympanum, and patients with a coagulopathy including those on blood thinning medications.²⁸ In patients with a minor trauma but a “high-risk” mechanism, cross-sectional imaging should still be considered. Although CT scans are highly sensitive for intra- and extra-axial hemorrhage, diffuse axonal injury cannot be seen on CT; instead, it must be diagnosed by surrogate markers such as diffuse cerebral edema and petechial brain hemorrhage.²⁹ Repeated CT scanning may be required in cases of clinical or neurologic change or deterioration, especially within the first 72 hours after injury.³⁰

Facial Imaging

Patients who suffer direct facial trauma should undergo specific facial CT scans in addition to a head CT.³¹ Other indications include deformity or instability of the maxillofacial structures found by physical exam; deformity, opacification, or fracture of the periorbital or paranasal sinus shown on head CT; and clinical evidence for leakage of cerebrospinal fluid.^{32,33} Certain facial soft tissue injuries have also been associated with facial fractures, and in patients with these injuries there should also be a higher suspicion for underlying facial fractures. These include lip lacerations, intraoral lacerations, periorbital contusions, subconjunctival hemorrhage, and nasal lacerations (LIPS-N).³⁴ CT is an excellent modality to detect occult fractures and to define displacements of fractures prior to operative intervention.³⁵ It does, however, deliver a significant radiation dose to both the orbits (associated with premature lens opacification) and the soft tissues of the neck including the thyroid. This should be considered especially when imaging children.^{36,37}

Neck Imaging

Blunt trauma to the neck can cause injuries to the aerodigestive tract including the esophagus, larynx, and trachea. Clinical findings include hemoptysis, hoarseness, crepitus, neck pain, abrasions, and hematomas. CT is the best imaging modality for these injuries; however, there are certain X-ray findings that may heighten suspicion of an injury such as soft tissue swelling, parapharyngeal or precervical emphysema, or larynx or hyoid bone fracture seen on cervical spine X-rays. In addition, patients with suspected injuries require contrast esophagoscopy, endoscopy, or both. A barium study should be performed to evaluate for an esophageal injury suspected above the carina, and a water-soluble contrast should be used for the distal esophagus or stomach. Aspirated gastrograffin is caustic to the airways, whereas intraperitoneal barium can lead to peritonitis.

Blunt carotid and vertebral injuries, although still relatively rare, are becoming increasingly more common likely due to a heightened awareness of the injury and increased

screening of asymptomatic patients. Cervical hyperextension and rotation, hyperflexion, and direct blows are mechanisms associated with these injuries.³⁸ Patients should undergo imaging if they have a cervical spine fracture (especially C1–C3 and fracture through the foramen transversarium), neurologic exam not explained by brain imaging, Horner's syndrome, LeFort II or III facial fractures, neck soft tissue injury, or an expanding cervical hematoma, as well as patients with blunt trauma presenting with epistaxis from an arterial source.^{39–41} Four-vessel cerebral angiography is the gold standard for diagnosis of these injuries; however, it is invasive and has risks associated including catheter insertion, hematoma, potential arterial pseudoaneurysm, renal dysfunction, and stroke risk. Therefore, CT angiography using MDCT is the test of choice for patients without obvious signs of vascular injury because it is rapid, noninvasive, and these patients are already undergoing other CT scans.⁴²

Spine Imaging

CERVICAL SPINE IMAGING

Cervical spinal imaging should be obtained for all trauma patients who have midline pain, tenderness on palpation, neurologic deficits, an altered mental status, intoxicated and in those patients with a distracting injury. Those patients who are awake with a GCS of 15, without neck pain, without midline cervical tenderness on palpation, tenderness on full range of motion, who do not have a distracting injury, and not intoxicated. These patients do not need to undergo radiographic imaging and may have their cervical spine collar removed.⁴³ Cross-sectional imaging of the cervical spine has largely replaced plain radiographs as the imaging modality of choice for suspected cervical spine injuries. These images should contain the occiput through T1 with sagittal and coronal reconstructions. Although not part of the initial trauma evaluation, MRI and flexion-extension X-rays are the preferred imaging modalities to evaluate for ligamentous injuries.⁴⁴

THORACOLUMBAR SPINE IMAGING

Similar to patients with cervical spine symptoms, those patients with back pain, thoracolumbar spine pain on exam, neurologic deficits, altered mental status including intoxication, distracting injuries, or a high-energy mechanism should undergo cross-sectional imaging of their thoracolumbar spine using an MDCT scanner.⁴⁵ In addition, those patients with a known cervical spine injury should also undergo imaging of their thoracolumbar spine. If patients are alert and evaluable and have a negative physical exam including lack of pain, tenderness to palpation, deformity, or neurologic deficit; low-risk mechanism; and are ≤ 60 years old, they may be cleared clinically without imaging because they are considered low risk for a thoracolumbar spinal injury.⁴⁶

CHEST IMAGING

A chest CT with intravenous contrast should be obtained in patients with suspected chest trauma, including a blunt

traumatic aortic injury.⁴⁷ In addition to the aorta, CT images can be used to evaluate the other great vessels, mediastinum, lungs, pleural cavity, and chest wall. For patients unable to receive contrast, a noncontrasted chest CT can diagnose a mediastinal hematoma. To help guide chest imaging, Blackmore et al. devised a protocol to determine who is at high risk to have an aortic injury. Any patients with two or more of the following are at high risk: > 50 years, unrestrained occupant in a motor vehicle collision, hypotension, evidence of thoracic injury, evidence of abdominopelvic injury, skeletal fractures, and brain injury.⁴⁸

ABDOMINAL/PELVIS IMAGING

Patients who are involved in a high-energy trauma with abdominal pain and tenderness or signs of trauma including abdominal bruising or a seat belt sign should undergo cross-sectional imaging of their abdomen and pelvis if they are hemodynamically normal and there is no other apparent indication for an emergency laparotomy. Patients with equivocal findings on physical exam, associated neurologic injury, or multiple extra-abdominal injuries should also undergo cross-sectional imaging of their abdomen and pelvis.⁴⁹ For patients with a suspected bladder injury, CT cystography or a cystogram is indicated. One of the disadvantages of CT scans is that they can miss bowel, pancreatic, and diaphragm injuries.

EXTENDED FOCUSED ASSESSMENT WITH SONOGRAPHY FOR TRAUMA (EFAST)

Point-of-care ultrasonography has been used in the trauma bay for the past two decades, and the Focused Assessment with Sonography for Trauma has become a standard of care.⁵⁰ It is a rapid diagnostic examination to evaluate patients who suffered blunt trauma with potential injuries to the torso and determine if there is fluid in the pericardial sac or the abdomen. Four areas are assessed: the pericardial sac; Morrison's pouch in the right upper quadrant, between the spleen and kidney; behind the spleen in the left upper quadrant; and the pelvis posterior to the bladder. This assessment is done sequentially and rapidly and detects intra-abdominal fluid as it accumulates in the dependent portions of the abdomen. It has been shown that in hemodynamically unstable patients who have suffered a blunt trauma, hemoperitoneum identified on FAST exam is sufficient to justify an immediate operation (Figure 60-1 and 60-2).⁵¹ The use of ultrasound to evaluate the thorax has also been demonstrated to be effective; it is immediately available, noninvasive, and highly sensitive. Therefore the FAST exam has been broadened to the Extended Focused Assessment with Sonography for Trauma (EFAST) to include evaluation of pneumothoraces.⁵² Ultrasound to diagnose injuries in patients suffering penetrating traumatic injuries has been studied less than blunt trauma, but has been shown to be effective in patients with a suspected

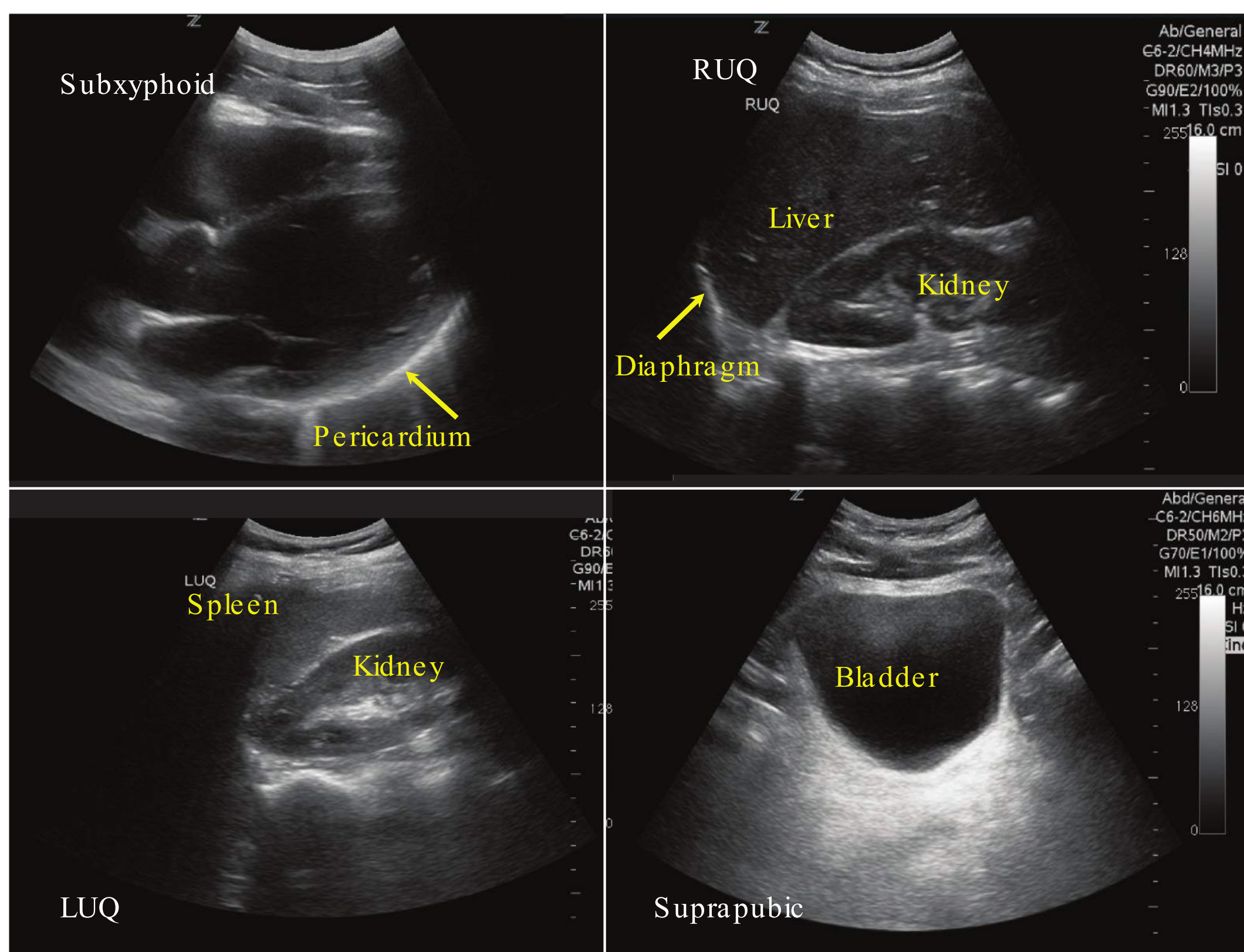


FIGURE 60-1 Normal FAST exam. (Used with permission from Ashika Jain, MD)

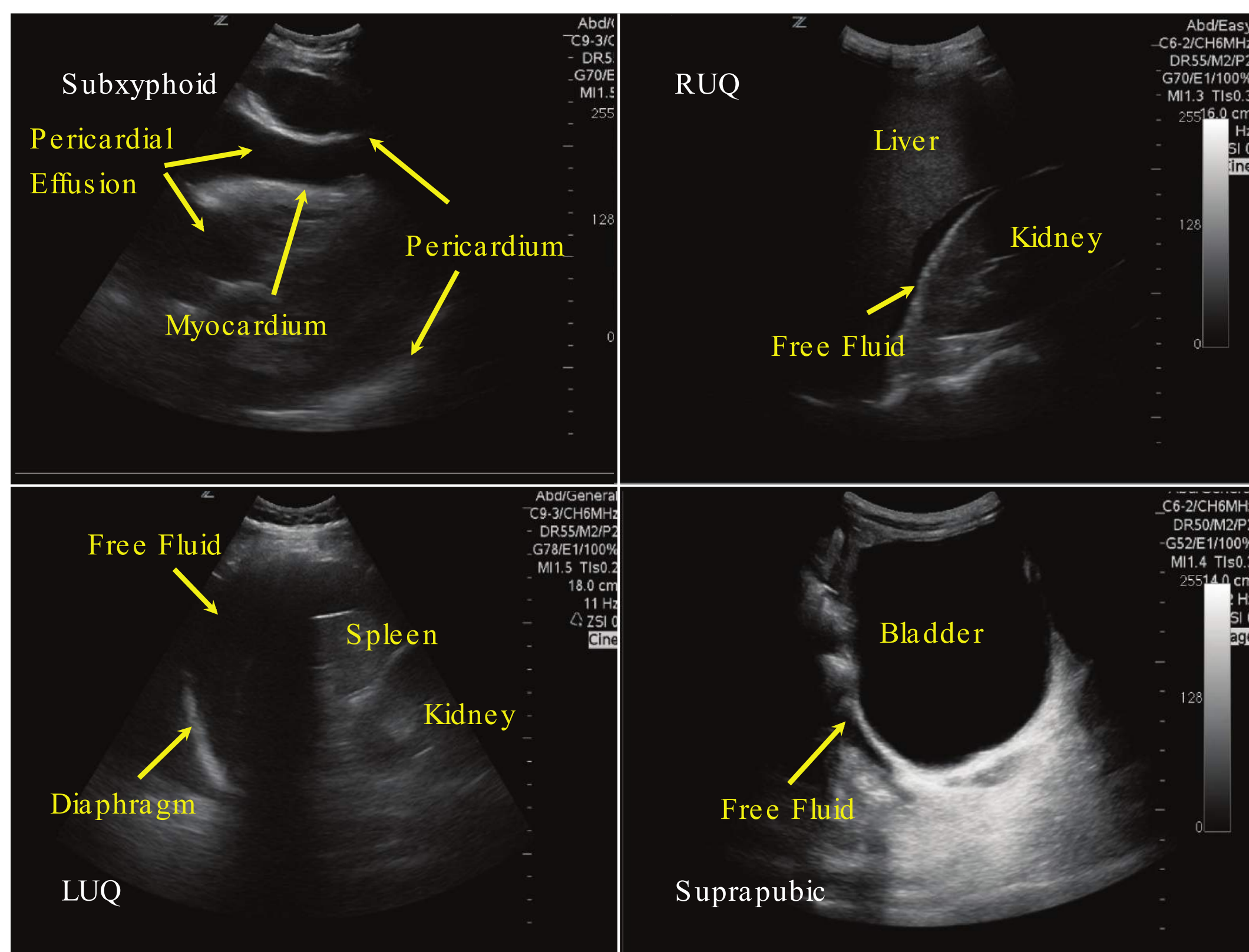


FIGURE 60-2 Positive images revealing free fluid during FAST exam, at the subxyphoid, Right upper quadrant, Left upper quadrant and Suprapubic. (Used with permission from Ashika Jain, MD)

penetrating cardiac injury.⁵³ Ultrasound has not been shown to be as reliable in penetrating abdominal trauma. It is recommended that patients with penetrating abdominal trauma should not be discharged from the emergency room based on a normal FAST exam.^{54,55}

CONCLUSION

Multisystem trauma patients are complex and require specialized care from the time of the injury throughout their hospital stay. The principals of ATLS should be followed, and patients are best cared for when the trauma team is prepared, well-organized, and able to communicate easily.

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Classification of Shock

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Herein lies the predominant secret of the regulation of the amount of oxygen consumed by the whole organism, determined only by the cell itself... arterial oxygen content, aortal pressure, velocity of blood stream, mode of respiration are all incidental and subordinate, they all combine their actions in the service to the cell.

—Pfluger 1872¹

INTRODUCTION

Shock clinically manifests as tissue hypoperfusion but fundamentally originates from inadequate cellular oxygen delivery or utilization. Phenotypically, the degree of “inadequacy” can vary among patients or even within the same patient. The clinical spectrum of hypoperfusion can be transient (i.e., vasovagal syncope), persistent with compensation (i.e., normotensive and tachycardic with small volume loss), or persistent and decompensated with cardiovascular collapse, multiorgan failure, and death.

Clinically, health care providers are alerted to intervene emergently when patients are hypotensive or are “not looking right.” Because shock is a time-sensitive diagnosis, recognizing and managing it early and closest to the onset of hypoperfusion portends the best prognosis.^{2–8} In general, definitive shock etiologies and their treatments are easier to classify retrospectively as more time and investigation unfold. Unfortunately, there are other times, acutely, when the exact etiology of shock may be multifactorial or undifferentiated thereby leaving providers to act with incomplete information. Regardless of circumstance, high-risk decisions need to be made to ensure acute stabilization and resuscitation, optimization, and prevention of organ dysfunction and death. The

intent of this chapter is to serve as a framework for providers to build on or refresh their confidence in understanding, diagnosing, and managing a wide array of shock states.

EPIDEMIOLOGY

Mortality from shock can be high and highly variable, ranging from 10% to 87%, depending on the type of shock, patient age, and comorbidities.^{9–12} There is no consensus definition for refractory shock although clinical trials often use 0.5 mcg/kg/min of norepinephrine or epinephrine as a threshold.¹³ Nearly 6% of critically ill patients will develop refractory shock, which accounts for 18% of deaths in intensive care units.¹³ Recent studies have examined this patient population. In a recent study, those patients requiring high-dose (≥ 1 mcg/kg/min norepinephrine equivalent) vasopressor (HDV) ($n = 443$) had significant 90-day mortalities (83%) with greater than half (58%) undergoing withdrawal of care.¹⁴ Of the few surviving to 90 days ($n = 76$), many (82%) went on to survive to 3 years and were younger than those who died before 3 years (53.1 vs. 64.8).¹⁵ When compared to other ICU illnesses, surveyed HDV survivors ($n = 36$) had similar rates of depression (19%), anxiety (39%), disability (36%), and full time employment (17%), and had lower post-traumatic stress disorder (8%).¹⁵ Taxonomically, shock etiologies have appeared similar between HDV survivors (sepsis 62%, cardiogenic 13%, cardiac arrest 7%, overdose 5%, hemorrhagic 3%, neurogenic 1%, pulmonary embolism 1%)¹⁴ and HDV patients who died (sepsis 54%, cardiogenic 11%, cardiac arrest 17%, overdose 3%, hemorrhagic 8%, neurogenic 1%, pulmonary embolism 3%).¹⁵

Emergency physicians (EPs) and critical care intensivists frequently encounter and are specially trained to manage acute critical illness. Nationally, 15.8% of ED patients are triaged as requiring immediate or emergent (within 15 minutes) care, whereas 11.5% of ED admissions go to the ICU.¹⁶ Nearly two-thirds of sepsis patients present through the ED (571,000 patients per year) with a mean ED length of stay (LOS) of 4.7 hours and 20.4% staying > 6 hours.¹⁷ Long-term, the ED volume of shock patients is anticipated to increase, given that the geriatric population aged ≥ 65 are on the rise and have traditionally accounted for more than half (58%) of patients with sepsis.^{10,18,19} Epidemiologic stratification delineating the types of shock presenting to the ED is largely speculative and under investigation.²⁰ A large ICU study of patients on vasopressors ($n = 1,679$) has shown the following shock distributions: distributive 66% (62% sepsis; 4% non-sepsis [neurogenic, anaphylaxis, overdose]), cardiogenic 16%, hypovolemic 16%, and obstructive 2%.^{21,22}

Shock Pre-Arrival and in the ED

A large multicenter US and Canadian Emergency Medical Service (EMS) study showed that one or more pre-arrival systolic blood pressures (SBP) < 100 mm Hg carried greater in-hospital mortality (US 26%; Canada 32%) than SBPs > 100 mm Hg (US 8%; Canada 11%).²³ Another EMS study examining a convenience sample of adult patients ($n = 673$) receiving a pre-arrival IV and lactate draw before any intervention showed that a lactate level of ≥ 2 mmol/L occurred in 46% of patients and was significantly associated with in-hospital mortality (adjusted OR = 3.57, 95% confidence interval [CI] 1.1–11.6).²⁴ Of the 673 patients, 11% were admitted to the ICU and 3.1% died in the hospital. A smaller EMS study showed patients with a pre-arrival lactate level of ≥ 4 mmol/L ($n = 61$) had an in-hospital mortality of 44.3% vs. 12.2% of patients ($n = 74$) with a lactate < 4 mmol/L.²⁵ Furthermore, subgroup analysis showed normotensive patients (mean arterial pressure [MAP] 60–90 mm Hg) with a lactate level of ≥ 4 mmol/L ($n = 27$) had a mortality of 35% versus 7% of patients with normotension and lactate level of < 4 mmol/L.²⁵

In the ED, the prevalence of hypotension (any ED SBP < 100 mm Hg) can be rather high (19%) as demonstrated from a random sample of admitted nontraumatic ED patients ($n = 4,790$).²⁶ This cohort had an 8% in-hospital mortality as opposed to 3% with the remaining admitted normotensive (SBP ≥ 100) patients ($p < 0.001$). Logistic regression revealed that exposure to hypotension was an independent predictor of in-hospital mortality (OR = 2.0, 95% CI 1.3–2.8). Furthermore, sustained hypotension (SBP < 100 mm Hg for ≥ 60 min) carried a 14% in-hospital mortality as opposed to a 5% in-hospital mortality with transient hypotension (only one SBP < 100 mm Hg with no others < 100 mm Hg). Additionally, the degree of hypotension also conferred a higher in-hospital mortality of 18% with an SBP < 80 mm Hg versus 5% if SBP was 90–99 mm Hg. In a different study examining this same cohort, investigators found that admitted patients with sepsis and nonsustained hypotension (≥ 1 SBP

of < 100 mm Hg but < 60 min) had a 10% in-hospital mortality versus 3.6% with no hypotension.²⁷

PATHOPHYSIOLOGY

A diagnosis of shock is based on clinical, hemodynamic, and biochemical signs.²² Traditionally, clinical signs have included ill appearance; poor color; extremes of respiratory or heart rates; weak pulse; decreased capillary refill; cold, clammy, or excessively warm skin; decreased urine output; or altered mental status. Hemodynamic alterations generally focus on hypotension (SBP < 90–100 mm Hg, MAP < 65, or a 40 mm Hg drop in SBP from baseline) but can also include extremes of chronotropy, inotropy, filling pressures, and vascular resistance. Biochemical abnormalities include laboratory values reflective of organ dysfunction (i.e., lactate, blood gases, creatinine, liver function tests, coagulation studies, thrombocytopenia, or inflammatory markers).

Clinically

“The Hippocratic facies, with the nose pinged, the eyes sunken, the temples hollow, the ears cold and retracted, the skin livid and cold, and the pulse feeble, characterizes the clinical features of circulatory shock.”²⁸ Unfortunately, due to diverse circumstances, many of these signs and symptoms—or their absence—prove to be unreliable gauges of the presence or degree of shock. Furthermore, different etiologies of shock often result in differing degrees of signs and symptoms. For instance, due to pathologic vasodilatation and excessive organ dysfunction, sepsis will account for a much more complicated array of signs and symptoms than those attributed to hemorrhage. Moreover, otherwise healthy individuals possess the ability to sustain a considerable loss of volume before exhibiting such obvious signs and symptoms, whereas a less healthy patient, or one with significant pre-existing comorbidities, may not be able to endure even a small volume loss without demonstrating serious signs and symptoms. In short, depending on the patient’s age, comorbidities, and clinical circumstances, shock may exist prior to the onset of evident signs and symptoms.

Biochemically

Regardless of etiology, shock as defined by cellular hypoxia denotes a state in which the anaerobic threshold is exceeded, intermediate metabolism through the Krebs cycle is blocked, and the emergency metabolic pathway is activated.^{28,29} Instead of pyruvate being aerobically metabolized in the mitochondria to generate ample energy (adenosine triphosphate [ATP]), it is metabolized in the cytosol by lactate dehydrogenase to generate lactate and excess hydrogen ions. In addition, phosphate is consumed and generates additional excess hydrogen ions.²⁸ Compared to aerobic metabolism, the net result of anaerobic metabolism is less potential energy (ATP), metabolic acidosis, and increased lactate in tissue and blood.

In regards to vasodilatory shock, the primary dysfunction is a failure of vascular smooth muscle to constrict, given that

plasma catecholamine concentrations are markedly increased and the renin–angiotensin system is activated.³⁰ Vasopressor resistance during these times has been attributable to three mechanisms: activation of ATP-sensitive potassium channels (K_{ATP} channels) in the plasma membrane of vascular smooth muscle, activation of the inducible form of nitric oxide synthase, and deficiency of the hormone vasopressin.³⁰

Mechanistically, K_{ATP} channels are physiologically activated, causing vasodilation via membrane hyperpolarization through decreased ATP, increased hydrogen ions, and increased lactate thereby linking cellular metabolism with vascular tone and blood flow.³⁰ Nitric oxide is a potent endogenous vasodilator and its production via inducible nitric oxide synthase has been shown in septic shock and decompensated hemorrhagic shock. Cytokine release, in part, is likely to induce nitric oxide synthase given that knockout mice without the gene encoding for inducible nitric oxide synthase have little hypotension in response to the administration of endotoxin.³⁰ Vasopressin is stored in the posterior pituitary gland and is released via osmotic control for water conservation or via baroreflex control for vascular smooth muscle constriction. Vasopressin levels have been shown to rise acutely during shock states but can be short lived (< 1 hour) and soon return to baseline levels, leaving a relatively deficient state.^{30–32}

Hemodynamically

Understanding shock requires understanding the concepts of oxygen delivery and global tissue hypoxia.³³

OXYGEN DELIVERY

Oxygen delivery (DO_2) is the total amount of oxygen bound to hemoglobin (Hb) and delivered to the peripheral tissues per minute.^{34,35} It is calculated as follows (see Figure 61-1):

$$DO_2 = CO \times CaO_2 \times 10$$

Although arterial oxygen content (CaO_2) is important, cardiac output (CO) is the most important determinant of oxygen delivery. As illustrated in Figures 61-2 and 61-3, CO has the ability to compensate for increases in metabolic needs or decreases in O_2 -carrying capacity. However, CO is a product of both heart rate and stroke volume (SV), and SV is affected by a multiplicity of factors. Thus, CO can be difficult to predict and manipulate.

- DO_2 = Oxygen delivery (DO_2) = Arterial oxygen content (CaO_2) \times cardiac output (CO) \times 10.
- $DO_2 = CO \times CaO_2 \times 10$
- $CO = HR \times SV$
- CaO_2 = Arterial oxygen content (CaO_2) = The amount of Hb available to bind O_2 , the amount of oxygen saturated Hb (SaO_2), and the amount of dissolved oxygen (PaO_2) in arterial blood. PaO_2 is usually ignored because the number is so small.
- $CaO_2 = (Hb \times SaO_2 \times 1.38) + (0.0031 \times PaO_2)$
- $DO_2 = CO \times (Hb \times SaO_2 \times 1.38) + (0.0031 \times PaO_2)$

FIGURE 61-1 Calculation 1.

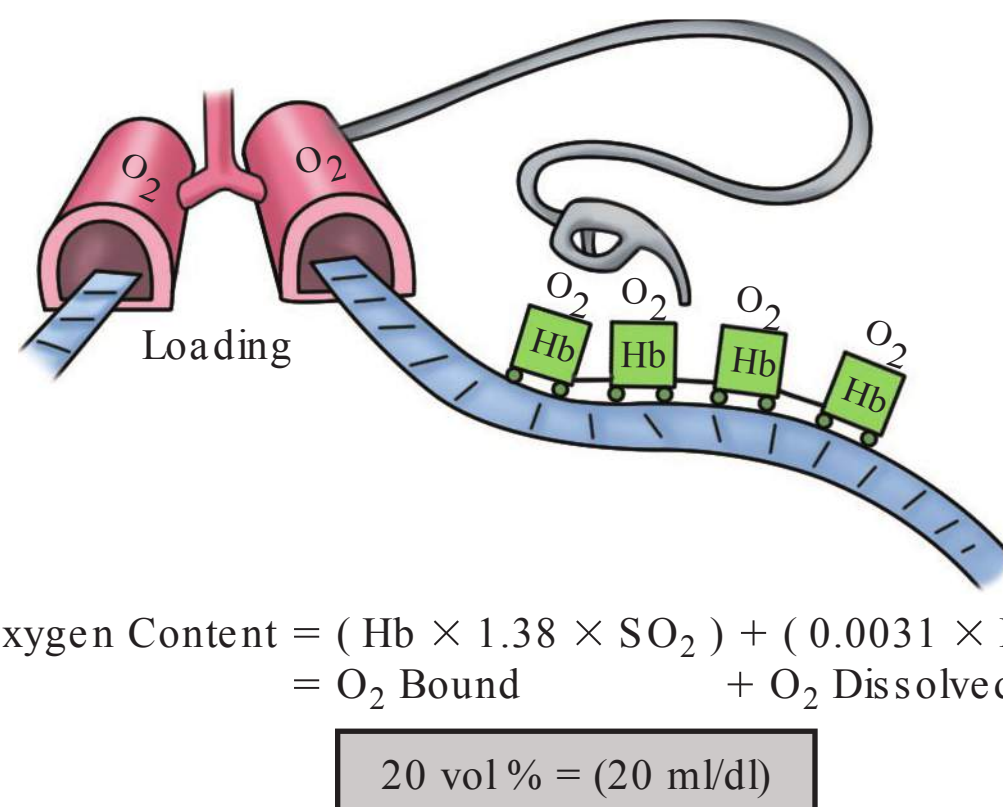


FIGURE 61-2 Oxygen delivery. Oxygen content is a function of bound oxygen (Hb) and unbound or dissolved oxygen. (Used with permission from Jeffery S. Vender, MD.)

Hg is another significant contributor to oxygen delivery. Because Hg is easily manipulated through transfusion, it becomes an important factor in regulating oxygen delivery. A schematic of a train may represent the impact of these components on the DO_2 system. How much oxygen is delivered to the tissues through the microvasculature depends on how many oxygen-carrying units (Hg) are present, how many of those Hg units are effectively carrying oxygen, and how effectively the heart is working to transport the oxygenated units. Once delivered to the capillaries, oxygen is offloaded from Hg and deoxygenated blood returns to the heart.

GLOBAL TISSUE HYPOXIA

Arterial oxygen saturation (SaO_2), measured as blood is ejected from the left side of the heart, is approximately 100%.

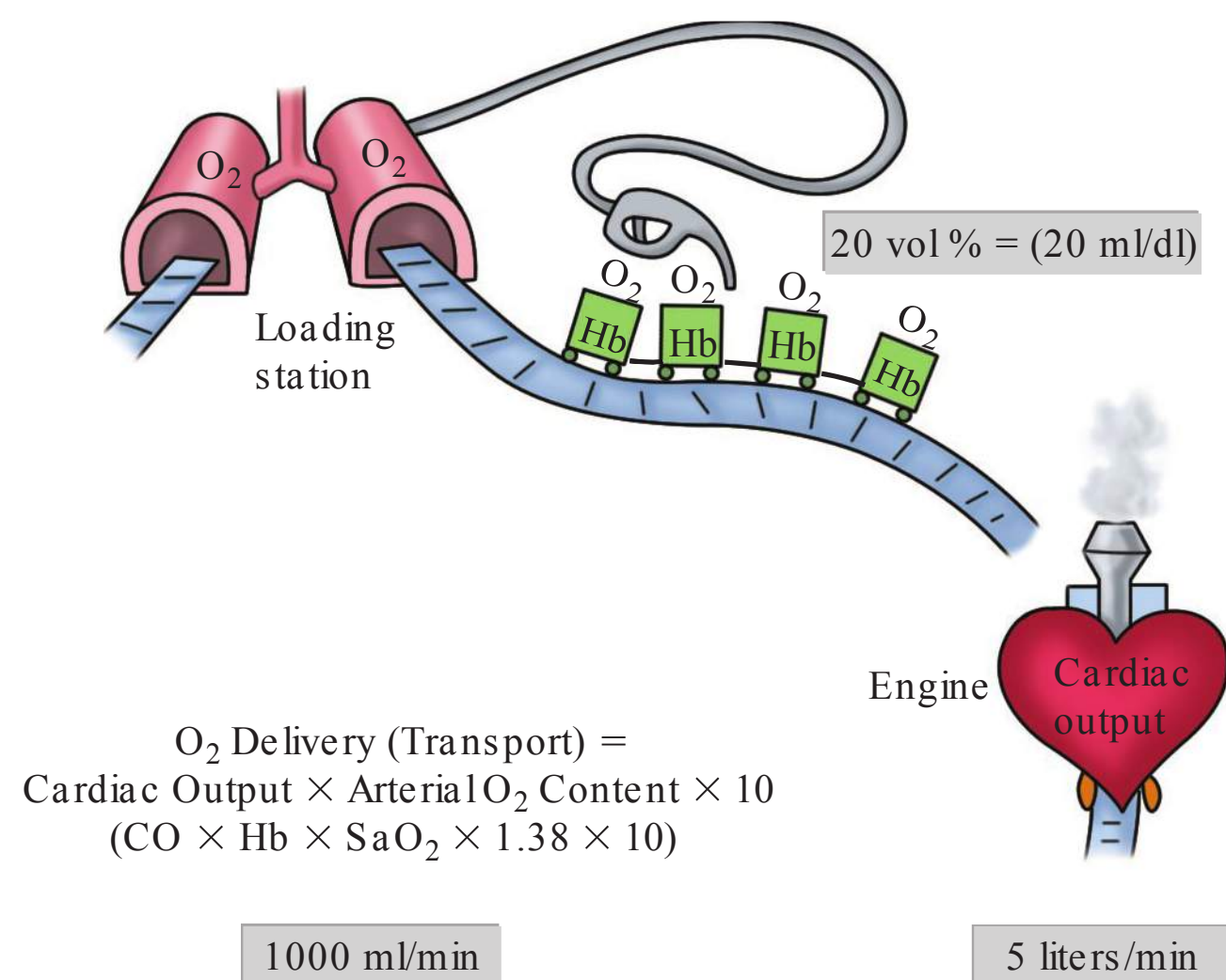


FIGURE 61-3 Oxygen delivery. Oxygen delivery is a function of cardiac output (CO), oxygen saturation (SaO_2), and hemoglobin (Hb). A disruption in any one of those components may adversely impact oxygen delivery. (Used with permission from Jeffery S. Vender, MD.)

As oxygenated blood circulates through the microvasculature, individual organs will have varying degrees of oxygen consumption (VO_2) and will therefore extract varying amounts of oxygen (i.e., 5–60%) depending on resting, adaptive, or pathologic conditions (Figure 61-4).^{35,36} In general, during

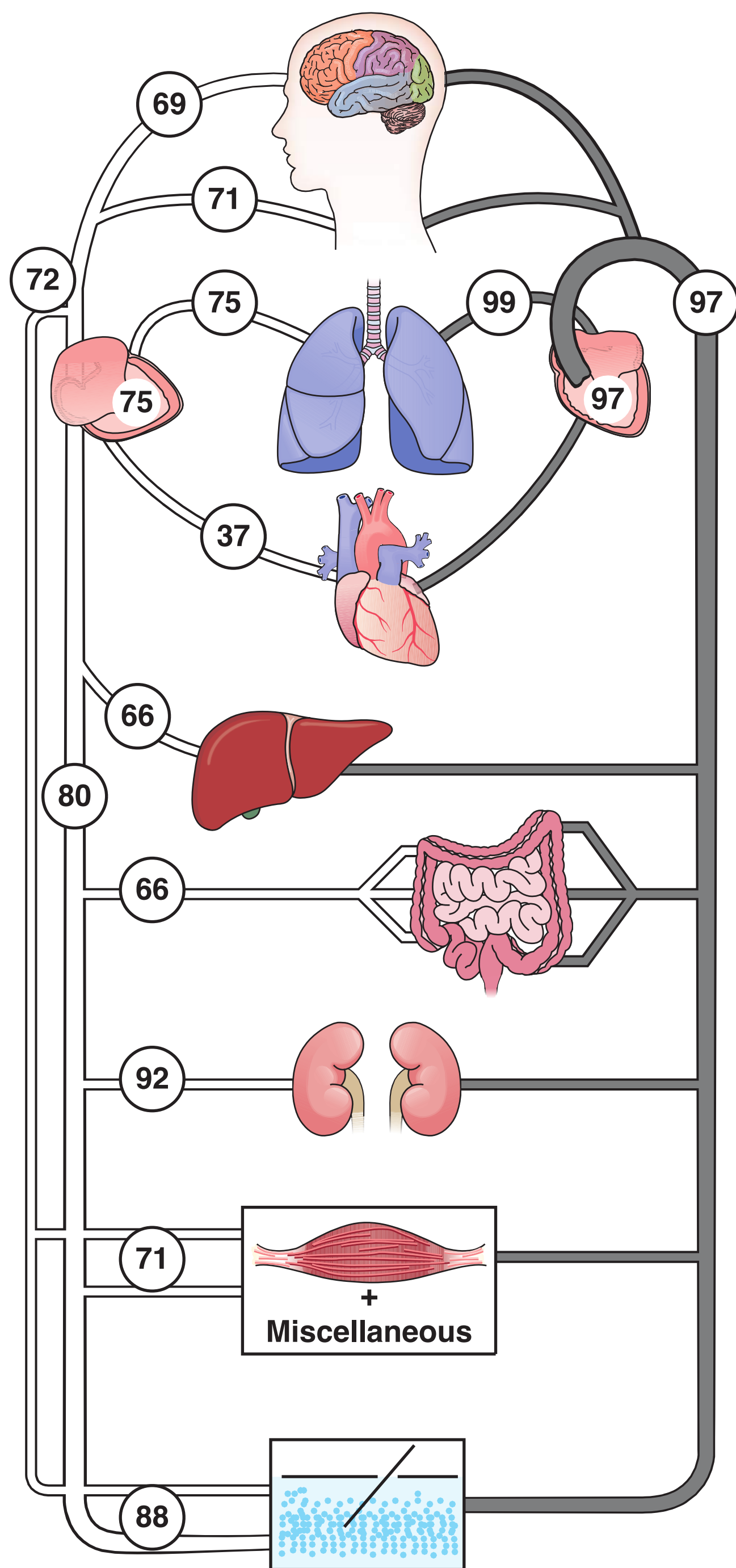


FIGURE 61-4 Percentages of arterial and venous oxygen saturations in various organ systems. v.c.sup., superior vena cava; v.c.inf., inferior vena cava. (Reproduced with permission from Reinhart K, Eyrich K: Clinical Aspects of O_2 transport and tissue oxygenation. Berlin: Springer-Verlag; 1989.³⁶)

a balanced delivery–demand state, the net average oxygen extraction by the peripheral tissues is 25%, leaving an aggregate pool of blood returning to the right heart with an oxygen saturation of 75% (Figure 61-5). This is best measured by evaluating the SvO_2 (mixed venous oxygen saturation) through a pulmonary artery catheter. However, because of efficacy and safety questions surrounding pulmonary artery catheters,³⁷ the measurement of ScvO_2 has been proved a functional surrogate,³³ and, because of logistics, ScvO_2 is a more practical and less morbid alternative in the ED and even ICU setting.

In cases of decreased DO_2 and mounting tissue hypoxia, compensation via increased oxygen extraction ($\text{SaO}_2 - \text{SvO}_2$) can occur to maintain aerobic respiration.³⁴ When the limits of oxygen extraction are exhausted, rises in serum lactate can be observed.³⁴ This critical threshold, where oxygen consumption becomes delivery- or “supply-dependent,” is termed the *critical DO_2* .^{34,38,39} Of note, heterogeneity in both disease state and the patient’s physiologic compensation can produce varying thresholds for critical DO_2 (Figure 61-6).⁴⁰

Clinically, when confronted with a supply-dependent shock state, management strategies include, but are not limited to, individualizing adequacy and balance among the components of oxygen delivery ($\text{DO}_2 = \text{CO} \times \text{CaO}_2 \times 10$):

1. Is there sufficient oxygenation?
2. Is there sufficient preload—does the patient require further fluid resuscitation?
3. Is there sufficient afterload or blood pressure for end-organ perfusion?
4. Is there sufficient chronotropy and inotropy?
5. Is the concentration of oxygen-carrying units optimal?
This is best assessed via a post-resuscitation Hg because the initial value may be significantly hemoconcentrated.

Once adequate oxygen delivery is assured, attention can be turned to assessing the remaining overall systemic balance between oxygen delivery and utilization–extraction.³⁴ Serial monitoring of lactate and ScvO_2 as a surrogate of SvO_2 can provide immediate and timely insights into early systemic imbalances of oxygen delivery and demand.²² Practically speaking, ScvO_2 is measured through a central line placed into the superior vena cava (SVC). This translates into the oxygen saturation report from a venous blood gas taken from the distal port of a typical internal jugular (IJ) or subclavian (SC) central line or from a continuous electronic readout from a central line with an appropriate sensor. ScvO_2 provides a measurement of global tissue hypoxia. For patients in shock, ScvO_2 is typically 5–7% higher than SvO_2 . Thus, ScvO_2 measurements < 70% may represent significant unresolved oxygen debts.³³

Although individual patients may vary, the general relationship of SvO_2 to tissue function is as follows:

1. $\text{SvO}_2 > 75\%$ = Normal extraction
2. $75\% > \text{SvO}_2 > 50\%$ = Compensatory extraction (increasing O_2 demand or decreasing O_2 supply)

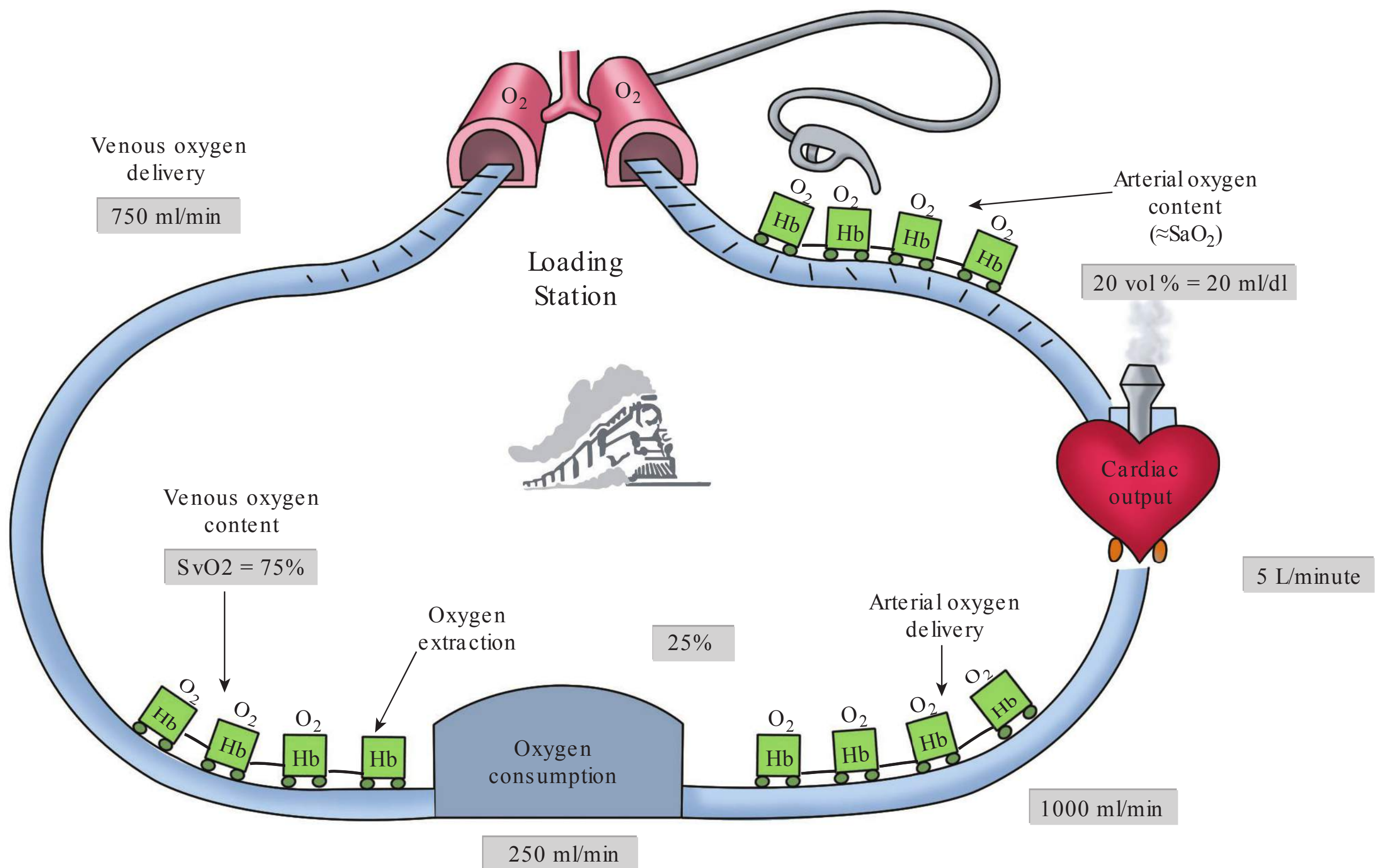


FIGURE 61-5 Oxygen delivery. At the level of the microvasculature, oxygen is extracted from the Hb and consumed by the tissues. Normally about 25% is extracted so that the oxygen saturation at the level of the heart (pulmonary artery, SvO₂; superior vena cava, ScvO₂) is about 75%. When SvO₂ or ScvO₂ is 70%, oxygen debt is occurring. (Used with permission from Jeffery S. Vender, MD.)

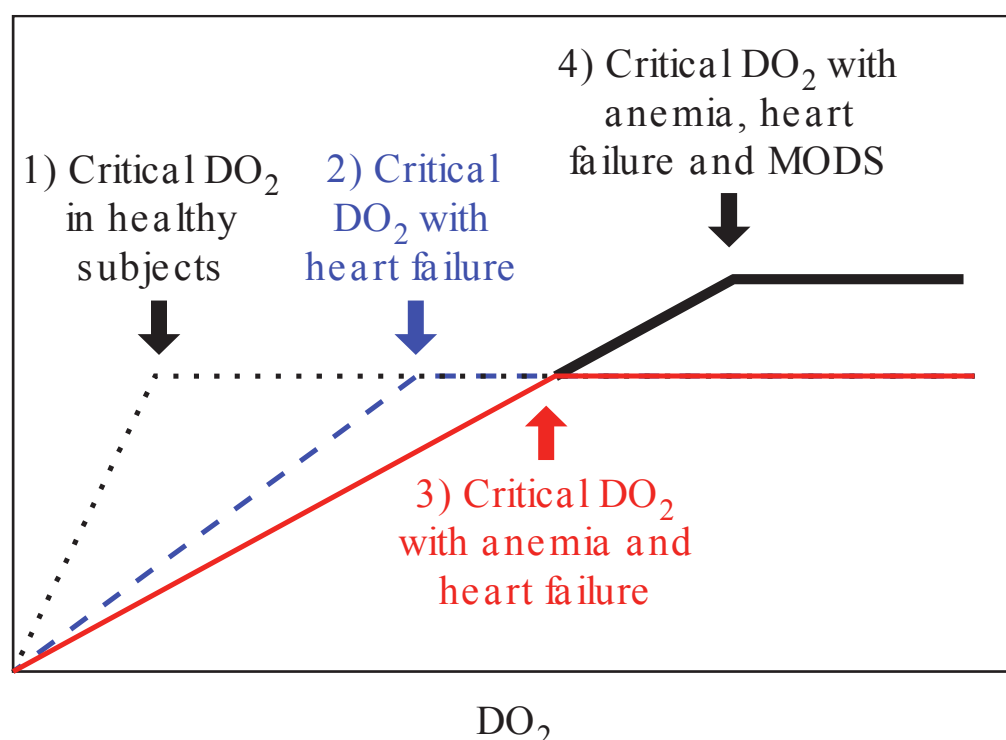


FIGURE 61-6 Critical oxygen delivery (DO₂) among various physiologic conditions. DO₂, oxygen delivery; VO₂, oxygen consumption; critical DO₂, level below which DO₂ does not meet oxygen demand (O₂ supply dependency). 1) In healthy subjects, as DO₂ decreases, VO₂ remains constant by compensatory mechanisms (increased cardiac output and cellular O₂ extraction; dotted black and white line). 2) Heart failure limits compensatory increases in cardiac output (hatched blue line). 3) Anemia and heart failure have further limitations because low hemoglobin decreases arterial oxygen content (CaO₂) (solid red line). 4) Severe cardiac dysfunction may be associated with systemic inflammatory response syndrome (SIRS) and multiple organ dysfunction syndrome (MODS), both of which increase systemic VO₂ and therefore critical DO₂ (solid black line). (Reproduced with permission from Du Pont-Thibodeau G, Harrington K, Lacroix J: Anemia and red blood cell transfusion in critically ill cardiac patients, *Ann Intensive Care*. 2014 Jun 2;4:16.⁴⁰)

3. 50% > SvO₂ > 30% = Exhaustion of extraction (beginning of lactic acidosis due to O₂ supply not meeting O₂ demand)
4. 30% > SvO₂ > 25% = Severe lactic acidosis
5. SvO₂ < 25% = Cellular death³⁴

Grouped conditions causing low venous oxygen saturations can be seen with decreased oxygen delivery (i.e., anemia, hemorrhage, hypoxia, hypovolemia, heart failure) or increased oxygen consumption (i.e., agitation, pain, fever, shivering, respiratory failure, increased metabolic demand).⁴¹ Conditions causing high venous oxygen saturations can be seen with increased oxygen delivery (i.e., oxygen, blood, fluid or inotrope administration, increased cardiac output) or decreased oxygen consumption (i.e., sedation, analgesia, hypothermia, mechanical ventilation, decreased extraction from shunting or cell death).⁴¹

Clinical Implications of Shock Pathophysiology

Traditionally SBP or MAP is used to denote shock (< 90 or < 65 mm Hg, respectively). This is based on the misconception that peripheral blood pressure universally equates to end-organ perfusion. Traditionally, shock has been defined or diagnosed at the point at which it could easily be identified

via vital sign aberrations. However, shock does not commence when blood pressure deteriorates; blood pressure deteriorates when the body can no longer compensate physiologically for oxygen debt not yet identified and/or addressed. *Cryptic shock*, also described as *normotensive shock*, refers to a physiologic state at the microvascular level resulting in accumulating oxygen deficit. Cryptic shock confers a high risk of morbidity and/or mortality.^{2,42–44} Biomarkers, in conjunction with vital signs and physical exam, assist in early identification. If developing shock is arrested prior to decompensation, significant mortality benefit is achieved. This concept is already established in hemorrhagic/traumatic,^{45–48} cardiovascular^{49–51} septic,^{2,4,52} and general critical shock presenting to the ED.^{53,54}

PHYSICAL EXAM, PRESENTING SIGNS AND SYMPTOMS

The presenting signs and symptoms of specific types of shock are presented elsewhere in this text. As with any emergent patient, whether in the ED, ICU, or deteriorating in a less monitored setting, airway, breathing, and circulation should be quickly assessed on presentation and intervened upon as necessary.

Vital signs should be checked frequently. This is a reality that cannot be overstated; in a scenario in which the patient is unstable, vital signs are, by definition, changing unpredictably. In the presence of such a dynamic situation, the repeated monitoring of vital signs may often translate into the difference between recovery and significant morbidity and/or mortality.

An initial set of vital signs should include blood pressure, temperature, heart rate, respiratory rate, oxygen saturation, fingerstick glucose, and electrocardiogram (ECG). The patient should be placed onto a cardiac monitor with frequent reassessments. A rectal temperature should be considered in all patients. Any vital sign abnormality is a clear indicator that further workup is warranted.

Any patient with clear or suspected shock requires a thorough physical exam, including the often omitted skin, back, urogenital system, and all orifices. Potential etiologies of shock should be considered during each component of the physical exam. Other chapters discuss specific elements of the exam. The following list is only a general reminder of elements to include or consider:

1. **General appearance.** “How does the patient look when I walk into the room?” The patient’s general appearance will direct the immediate plan of action.
2. **Mental status and full neurologic exam.** Altered mental status refers to a wide spectrum from confusion to coma. Mild, new confusion may be an early indicator of an ominous process, especially in the elderly. A complete neurologic exam should be performed. When the neurologic exam is limited, radiographic assessment may be required.
3. **Head, ears, eyes, nose, and throat.** An oral process is a potential septic source frequently overlooked.

4. **Neck.** Hypotension with full neck veins requires consideration of a cardiac etiology, and hypotension with flat neck veins may indicate a systemic origin. Furthermore, consideration should be given to an infectious or traumatic process contributing to the presentation. Swelling that causes tracheal deviation may be due to a pharyngeal abscess. In the setting of trauma, tracheal deviation may be due to hemorrhage, and crepitus may be due to a laryngeal fracture. Furthermore, a cervical spine fracture may lead to neurogenic shock.
5. **Chest/heart/lungs.** Potential etiologies that may manifest acutely as shock include but are not limited to acute myocardial infarct, pulmonary embolism, pericardial tamponade, myocarditis, tension pneumothorax, and/or pneumonia.
6. **Abdominal exam.** An extensive evaluation in conjunction with the history for physical manifestations of multiple diseases is important. Considerations include but are not limited to vascular insufficiency, bowel perforation, cholangitis, hemorrhage, and perforated peptic ulcer. Radiographic exam is often necessary. Notably, an unimpressive abdominal exam does not rule out a significant insult; notoriously, the elderly may present with a seemingly unimposing exam while harboring significant pathophysiology.
7. **Urogenital exam.** A complete urogenital exam will prevent missing important causes of toxic shock syndrome such as intrauterine devices and tampons or sepsis due to Fournier’s gangrene in a diabetic patient.
8. **Back.** If the back has not been evaluated, only half of the patient has been examined. In patients using intravenous drugs, consider an epidural abscess.
9. **Rectal exam.** Evaluation may include but should not be limited to perirectal abscess, blood, and foreign body.
10. **Skin.** Septic shock may be from cellulitis or an unrecognized infected joint, decubitus ulcer, or endocarditis. Especially in obese patients in whom heart sounds can be difficult to auscultate, it is even more important to check hands, feet, and nail beds.

CLASSIFICATION AND MANAGEMENT

The clinical utility of the differential diagnosis of shock is based on understanding differences in effective tissue perfusion. Shock can be divided into four categories: *hypovolemic*, *distributive*, *cardiogenic*, and *obstructive* shock. Poor venous return is the base etiology of hypovolemic (absolute reduced intravascular volume) and distributive (ineffective vasomotor tone, relatively reduced intravascular volume) shock. Cardiogenic shock is due to pump failure, so while there may be adequate intravascular volume, there is inadequate circulating volume. Finally, obstructive shock is due to a structural impediment of blood flow through the cardiac circuit. Additionally, there are mixed forms of shock with various overlaps of the given categories.^{22,28,55}

Four management strategies can be considered when treating shock: *salvage*, *optimization*, *stabilization*, and *de-escalation*.²² The *salvage* phase focuses on obtaining a minimal blood pressure (MAP > 65) and performing case-specific emergent life-saving interventions (i.e., oxygen administration and airway stabilization, thoracostomy, pericardiocentesis, thrombolysis, administration of intravascular volume, vasopressors, antibiotics, source control, surgery). The *optimization* phase focuses on trending and maintaining oxygen delivery and utilization. Vital sign and clinical exam improvements are minimal goals but may not reflect ongoing occult organ dysfunction. For this reason, trending of additional resuscitation end points include but may not be limited to monitoring lactate clearance, urine output (> 0.5 mL/kg/hr), ScvO₂, and cardiac output. The third phase is *stabilization*, and its focus is on providing continued organ support while minimizing complications. Last, the fourth phase is *de-escalation* with the goal of titrating supportive care as tolerated and achieving a negative fluid balance.²²

A Systematic Approach to Shock States

All shock states require confirmation that oxygen delivery is meeting demand. Interventions and procedures are based on the type of shock suspected. However, not all facilities are equipped to deal with patients in shock. Thus, transfer to an ICU or to an ED that has more resources may be necessary. In general, the same ED systematic approach of IV, O₂, monitor, airway, and ultrasound equipment to the bedside are employed when encountering an acutely deteriorating shock patient. These fundamental principles were recognized in 1969 by Dr. Weil in his mnemonic “VIP-PS”: Ventilate (deliver oxygen), Infuse (intravascular volume), Pump (vasoactive agents), Pharmacologic (medications), Specifics/Surgical (medical and surgical management of the primary cause).^{22,56} For the acutely deteriorating or undifferentiated shock patient, a modern ED approach to the VIP-PS principle would be the “ABCDEFs” of resuscitation or primary survey (Airway, Breathing, Circulation, Disability, Exposure, Frequency [Ultrasound-FAST, eFAST, RUSH]).^{57,58}

- *Airway*. If there is any doubt, secure the airway. Stabilization goals are unchanged (correction of hypoxia and/or hypercarbia) except for the hemodynamic caveat of ensuring adequate blood pressure pre-/post-intubation given the very high risk of peri-intubation arrest.^{59,60}
- *Breathing*. With Once, airway is secured, confirmation via colorimetric or wave form capnography to ensure correct placement of endotracheal tube. Use of lung protective strategies (i.e., lower tidal volume 6 mL/kg ideal body weight, peak/plateau pressures < 30 cm H₂O for ARDS or at-risk parenchyma) to avoid hypoxia, hyperoxia, or excess hypercarbia.^{61,62}
- *Circulation*. Given no significant short-term differences in mortality, fluid administration can be crystalloid or colloid (avoid starches with sepsis, avoid colloids in brain-injured patients).^{31,63,64} When possible, volume administration should be guided by a dynamic response to an objective measure (i.e., stroke volume, cardiac

output, pulse pressure variation, systolic pressure variation, stroke volume variation, heart rate, blood pressure, shock index, vena cava collapsibility, ventricular chamber size, urine output, clinical improvement).^{31,65–69} Patients with distributive shock such as sepsis can commonly tolerate initial fluid boluses of 20–30 mL/kg. However, until cardiogenic involvement is ruled out (i.e., bedside ultrasound and ECG), frequent reassessments after 500 mL boluses or with a passive leg raise is prudent.^{2,5,70} For nonhemorrhagic hypovolemic shock, if blood pressure goals (MAP > 65, SBP > 90) are unable to be obtained with volume, the initial vasopressor choice is generally norepinephrine given that dopamine has been associated with increased mortality in cardiogenic and septic shock.^{21,71} Permissive hypotension and blood product replacement would be the primary approach for traumatic hemorrhagic shock.⁷² If nonobstructive shock persists with decreased cardiac contractility despite adequate oxygenation, preload, afterload, and hemoglobin goals being met, consideration should be given to inotropic support (i.e., dobutamine).

Noninvasive tests depend on the type of shock suspected. Most cases will require ECG, X-ray, pulse oximetry, and continuous vital sign monitoring. The role of ultrasound is rapidly expanding beyond the standard extended focused assessment for trauma (eFAST), which is sensitive and reliable in the assessment of trauma patients. Ultrasound applications such as examination of ventricle size, estimation the ejection fraction, and determination of the collapsibility of the inferior vena cava are sensitive in cases of differentiated and undifferentiated shock.^{58,73–79} If the patient is sufficiently stable to leave the department, further noninvasive diagnostic testing is based on suspected shock etiology, such as CT for blunt trauma or PE.

Laboratory testing should also be based on the type of shock but generally includes chemistry, complete blood count (CBC), coagulation profile, troponin, lactate, arterial blood gas, central venous blood gas (if continuous ScvO₂ monitoring is not available), urinalysis, and cultures of blood and urine. Additional labs may include liver function tests, thyroid function tests, base deficit, toxicology screening for medications or drugs of abuse, and an ethanol level. General practice procedures for all forms of shock include central line and arterial line placement. A central line is indicated for the administration of vasopressors, measurement of central venous pressure (CVP) as indicated,⁸⁰ measurement of ScvO₂ (preferably SC line or IJ line), multiple ports for infusions, or an inability to establish sufficient peripheral intravenous accesses. Arterial line placement is used for continuous arterial blood pressure monitoring and should be considered in all hypotensive patients requiring vasopressors.

Hypovolemic Shock

Hypovolemic shock is due to decreased intravascular volume, leading to decreased preload and CO, resulting in reduced oxygen delivery. Potential etiologies include dehydration, hemorrhage, vomiting, severe burns, and iatrogenic sources

such as diuretics and vasodilators. The CRISTAL study examining hypovolemic shock in the ICU ($n = 2,857$) showed the following case mix and corresponding mortalities: sepsis 54% (29% mortality), trauma 6% (15% mortality), and non-sepsis/non-trauma 40% (25% mortality).⁶⁴

Hypovolemic shock can be recognized clinically by tachycardia, tachypnea, hypotension, narrow pulse pressure, altered mental status, decreased venous pressure, decreased urine output, and capillary refill. These signs and symptoms are derived from the lack of baroreceptor activation, which tends to increase heart rate and contractility coupled with a lack of stretch receptor activation in the atria leading to reduced release of atrial natriuretic peptide. Other acute changes that occur include activation of the renin–angiotensin–aldosterone system, mediated by the kidney. Angiotensin causes two main responses: vasoconstriction of the arteriolar smooth muscle and secretion of aldosterone, which promotes sodium reabsorption and water retention that results in extreme thirst. Often, these clinical symptoms are not recognized until 10–20% of whole blood volume has been lost. Importantly, it is possible for children to compensate for loss of volume for a longer period of time than adults (blood pressure maintenance despite hypovolemia). However, when decompensation commences, clinical decline is extremely rapid, often with poor outcomes.

Estimated circulating blood volume for adults is 70 mL/kg; for pediatrics it is 80–90 mL/kg.⁸¹ The 2012 *Advanced Trauma Life Support (ATLS) Student Manual* 9th edition provides a structured blood loss classification scheme outlining progressive clinical and vital sign derangements with greater percentage of blood loss: Class 1 = < 15%; Class 2 = 15–30%; Class 3 = 30–40%; Class 4 = > 40%.⁸¹ Of note, tachycardia (HR > 100) is reported to begin with Class 2 (\approx 20% blood loss), whereas hypotension can begin with Class 3 (\approx 30% blood loss). Additionally, this scheme may have some limitations because individual patient physiology varies, and several studies have shown little to no agreement in the predictive interdependence of heart rate, respiratory rate, SBP, and Glasgow Coma Scale (GCS) when using the ATLS blood loss classification system.^{82,83}

In the acute phase, crystalloids or colloids can be used for initial volume replacement as outlined earlier for hypovolemic shock.⁶⁴ The Surviving Sepsis Campaign suggests albumin use (no starch) in the fluid resuscitation of severe sepsis and septic shock when patients require substantial amounts of crystalloids (Grade 2C recommendation).³¹ ATLS initial fluid recommendations are to administer 1–2 L of warm crystalloid and to consider blood product replacement thereafter for persistent hypotension while continuing to search for and control any ongoing bleeding.

Cardiogenic Shock

A 23-year review published in 1999 demonstrated that, on average, there was a 72% in-hospital mortality and 7.1% incidence of cardiogenic shock with acute myocardial infarction (AMI).⁸⁴ Cardiogenic shock results from significant “pump

failure” that may occur due to valvular pathology, myocardial insult, or pericardial pathology. Depending on patient reserve, for myocardial etiologies, cardiogenic shock may occur when 40% of the myocardium is compromised, due usually to toxins, ischemia, or immune or inflammatory processes.⁵⁵ The reduction in effective CO results in decreased DO_2 . The clinical manifestation may appear similar to hypovolemia (see earlier discussion), except that the patient may have jugular venous distension (due to increased jugular venous pressure) and a pulmonary exam consistent with edema (due to fluid backup resulting from inefficient pumping of the heart). Additionally, there may be cardiac sounds such as a new murmur or ECG changes that may guide resuscitation. Diagnosis of cardiogenic shock can be made by clinical findings (as presented earlier); radiologic findings, which may show poor ventricular function or ventricular septal rupture on echocardiography; or ECG findings, which may demonstrate arrhythmias or signs of ischemia.

Initial treatment for cardiogenic shock often consists of carefully chosen combinations of vasopressors and inotropic agents. Vasopressors cause vasoconstriction, whereas inotropic agents increase the force of cardiac contraction, depending on which receptors are stimulated by these medications. The goal is to increase perfusion of the ischemic myocardium. In the particular case of cardiogenic shock, however, extreme heart rates must be avoided due to increased myocardial oxygen consumption, which may further impair cardiac function and worsen the cardiogenic shock. In addition, there is the potential for increasing permanent damage to the heart (by increasing infarction size or causing valvular dysfunction). Short-acting inotropes, such as dobutamine, dopamine, or norepinephrine, should be considered, while longer-acting agents such as milrinone should be used with caution. Of note, dopamine has been shown to increase mortality in patients with cardiogenic shock.²¹ A small randomized controlled (RCT) trial of ICU patients ($n = 30$) with cardiogenic shock showed that global hemodynamic effects were similar between epinephrine and norepinephrine-dobutamine. Nevertheless, epinephrine was associated with a transient lactic acidosis, higher heart rate and arrhythmia, and inadequate gastric mucosa perfusion. This small study concluded that the combination of norepinephrine-dobutamine appeared to be a more reliable and safer strategy.⁸⁵ Cautious fluid administration might be considered as required to maintain preload and thereby CO, but this must be monitored carefully. In cases of myocardial infarction, rapid definitive treatment of coronary artery reperfusion should be sought. When rapid transport to a cardiac catheterization laboratory is not possible, chemical thrombolysis and/or mechanical device support such as an intra-aortic balloon pump (IABP) should be considered. Additionally, in appropriate cases, a left ventricular assist device (LVAD) may be a necessary bridge to cardiac transplant.

Obstructive Shock

Obstructive shock is an extracardiac obstruction resulting in decreased diastolic filling or decreased ejection fraction.

Usually both diastolic filling and decreased ejection are involved, with one predominating. Decreased CO occurs from decreased diastolic filling such as occurs in restrictive pericarditis and cardiac tamponade. Muffled heart sounds and/or distended neck veins may signify cardiac tamponade. Pericardial friction rub is the pathognomonic sign of pericarditis. Decreased CO is also seen—immediately—with large pulmonary emboli. A large pulmonary embolus (or multiple smaller ones) decreases the cross-sectional area of blood flow from the right ventricle to the left atrium causing right ventricular overload and leading to right ventricular failure. The clinical presentation is similar to that of cardiogenic shock with hypotension and IJ distension but without pulmonary edema. Unilateral calf swelling or erythema may denote a deep venous thrombosis (DVT) that could be the source of a pulmonary embolus. Decreased breath sounds and/or tracheal deviation are tell-tale signs of tension hemo-/pneumothorax.

While most forms of obstructive shock require a rapid clinical diagnosis and immediate intervention, there are some adjunctive diagnostic tests that may aid in refining the assessment. If available, bedside cardiac and lung ultrasound provide a rapid means for evaluating cardiac tamponade, right ventricular involvement from pulmonary embolism (i.e., disproportionate enlargement to LV, hypokinesis, septal bowing), or hemo-/pneumothorax (as evidenced by fluid or air signal on lung sonography). Chest X-ray may also reveal a hemo-/pneumothorax, deviated trachea, or widened mediastinum. EKG can reveal low voltage amplitudes or electrical sequelae of pericarditis (ST elevation, inverted T waves) or pulmonary embolism (tachycardia, S1Q3). Contrast computed tomography (CTA) of the chest or pulmonary ventilation/perfusion (V/Q) scan can reveal pulmonary embolism.

The treatment of obstructive shock requires treatment of the underlying condition along with supportive care. Hemo-/pneumothorax is treated by decompression of the chest with a thoracostomy tube; cardiac tamponade requires decompression of the pericardium with needle pericardiocentesis or a pericardial window. Pulmonary embolism requires systemic anticoagulation or occasional procedural intervention with directed lysis or surgical removal of the large clot. Vasopressor support is often necessary, as is ventilator support in patients with respiratory failure.

Distributive Shock

Distributive shock is due to significant vasodilatation that causes decreased preload and afterload. In the arterial bed, it manifests through decreased arterial resistance, causing hypotension. Distributive shock may arise from circumstances such as sepsis (most common), anaphylaxis, adrenal insufficiency, and neurogenic shock. Other causes for vasodilatory shock include any prolonged and severe hypotension, intoxication (carbon monoxide, metformin, nitrogen, cyanide), and some mitochondrial diseases.³⁰

Initially, septic shock typically presents as hypovolemia due to both vasodilatation (distributive shock) and leaking capillary membranes (hypovolemic shock). However, a

distinguishing clinical feature is significantly more intravenous fluid requirement. It is not uncommon for distributive shock patients to have a 6- to 10-L fluid deficit and still require vasopressors to maintain a reasonable mean arterial blood pressure ($\text{MAP} \geq 65 \text{ mm Hg}$).⁸⁶ Once the fluid deficit is abated, the typical manifestations of distributive shock, such as high CO, low systemic vascular resistance (SVR), and hypotension, emerge. Interestingly, although the patient in distributive shock exhibits a high CO, it can occur paradoxically in conjunction with a depressed myocardium. Inflammatory mediators cause myocardial depression so that the heart pumps less efficiently. The myocardial depression results in a depressed biventricular ejection fraction. In response to volume loading, the stroke work index is further reduced. However, it appears that, simultaneously, the ventricles dilate. The dilatation, in conjunction with an increased heart rate, provides the increased cardiac index (CI). This may actually be protective, as nonsurvivors who were unable to attain LV dilatation have been observed to die from cardiogenic complications of septic shock.⁸⁷ The incidence of septic cardiomyopathy in several studies has been estimated at 18–29% at 6 hours, 46% at 12 hours, 60% after the first day.⁸⁸ Although, without mention of echo findings and potentially shrouded in partial inotropic effects from vasopressors, ED studies have indirectly hinted at this finding via documented dobutamine use ranging from 1–14%.^{2,4,5} Furthermore, some studies have shown both LV functional and mortality improvements in patients who are responsive (i.e., improved oxygen extraction) to dobutamine administration.^{88,89}

In the end, although distributive shock manifests with a normal or increased CO, it is functionally ineffective due to maldistribution of blood flow caused by shunting either from or within an organ, such that the organ, either in part or whole, may be compromised. A common clinical example is a septic patient who has normal or increased CO but is in acute renal failure. Clinically, distributive shock may manifest as a hyperdynamic, high-flow state with hyperdynamic heart sounds, prominent and rapid pulses, quick capillary refill, and a wide pulse pressure.

Mixed Shock

Although it would be helpful if all patients presented in a specific isolated type of shock, frequently there is significant overlap requiring solid clinical acumen. On occasion, patients will present with multisystem trauma and have a mix of hemorrhagic, obstructive, and neurogenic shock etiologies. Furthermore, primary or secondary endocrinopathies (i.e., pituitary, thyroid, adrenal, vasopressin) or vitamin abnormalities (B, C, D) can affect hemodynamic and homeostatic stability.^{31,90–92} But perhaps the most common disease state to cause and complicate mixed shock presentations is sepsis. A retrospective ED study examining a convenience sample of patients ($n = 571$) with an initial lactate level of $\geq 4 \text{ mmol/L}$ showed 50% to have sepsis.⁹³ The CRISTAL study showed that 54% of hypovolemic shock patients had sepsis.⁶⁴ An ED prospective observational study ($n = 173$) of adult

out-of-hospital cardiac arrests (OHCA) found 38% to be bacteremic, with asystole and PEA as the most common presenting rhythms. Mortality in the ED was significantly higher in bacteremic OHCA (75.4%) compared to non-bacteremic OHCA (60.2%, $p < 0.05$).⁹⁴ The mixed shock presentation of sepsis can involve the following:

- *Hypovolemic shock.* Septic shock patients presenting with a lactate level of ≥ 4 commonly have a 6- to 10-L fluid deficit. Aggressive fluid administration and serial reassessment is a mainstay of initial treatment.
- *Distributive shock.* Bacterial-derived mediators in the septic shock patient, such as endotoxin, along with components of the inflammatory cascade, cause distributive shock with low SVR early in the presentation and normal to high CO in later stages.
- *Cardiogenic shock.* Although the typical description of septic shock is high CO in the face of a low SVR, early septic shock frequently manifests as a low CO/CI state consistent with hypodynamic, cardiogenic shock. In the early goal-directed therapy (EGDT) study of Rivers et al., the average time to enrollment was 1 hour, with low CIs ranging between 1.7 and 2.9.² Depressed myocardium persisted even after fluid resuscitation, implying myocardial dysfunction rather than a factor of decreased preload as the etiology of a low CI. The high CO state arises after the compensatory dilatation of the ventricles, as described earlier in the section “Distributive Shock.”⁸⁷ The inflammatory response of any of these forms of shock, especially distributive, may result in multiple organ dysfunction syndrome (MODS). Often at this time, the only therapeutic options left are supportive, with many patients refractory to the support.

Cryptic Shock: Support for Early Recognition and Treatment

Shock must be recognized before it can be treated. Fulminant or late forms of shock manifesting with hypotension are not difficult to identify. Diagnosing shock before physiologic deterioration is a far greater challenge. However, significant improvements in morbidity and mortality can be achieved with early recognition of biochemical or cryptic shock that manifests as physiologic deterioration on a microvascular level, prior to deterioration of global parameters such as blood pressure.

- *Cryptic shock in severe sepsis and septic shock.* The EGDT trial demonstrated an absolute mortality benefit of 16% when septic patients who were hypotensive after a fluid bolus and/or had a lactate level of ≥ 4 mmol/dL were treated under a protocol that normalized CVP, blood pressure, ScvO₂, and lactate. Additional studies treating severely septic patients (lactate ≥ 4 mmol/L) with quantitative resuscitation strategies have shown reduced mortalities.^{4,5,7} One study showed that normotensive patients not normalizing their lactate by 6 hours can have mortalities as high as 55%.⁵² In the ED, lactate nonclearance can be relatively infrequent (9%) but still

carries a high mortality (60%) versus those having lactate clearance (19% mortality, $p < 0.001$).⁹⁵ A curvilinear lactate–mortality relationship has been observed such that incremental lactate elevations can progress from a 6% mortality with a lactate level of < 1.0 mmol/L to 39% for a lactate level of 19–20 mmol/L.⁹⁶ On the other hand, 10% interval reductions of lactate can carry 11% reductions in mortality.⁵² Greater clearance appears to confer greater rates of survival, with one study showing that patients with a $> 36\%$ lactate clearance had a 30-day mortality of 10.7% versus 61.1% mortality for those with $< 36\%$.⁹⁷

Normotension does not always equate with guaranteed survival. Normotensive cryptic shock patients with lactate levels of ≥ 4 mmol/L treated with quantitative resuscitation can have mortalities (20%, 95% CI 11–34) that mirror the mortality of hypotensive patients (19%, 95% CI 15–25).⁹⁸ Normotensive patients with intermediate lactate (2.0–3.9 mmol/L) also carry increased risk of death, as shown in a systematic review demonstrating a 14.9% mortality with a range of 3.2% to 16.4%.⁹⁹

In prognosticating between lactate normalization or clearance, one RCT of patients who received quantitative resuscitation showed lactate normalization (< 2 mmol/L) to be the strongest predictor of survival (adjusted OR = 5.2; 95% CI 1.7–15.8), followed by lactate clearance of $\geq 50\%$ (OR = 4.0; 95% CI 1.6–10.0).¹⁰⁰ From a hemodynamic perspective, one ED study showed that vasoplegic shock patients (SBP < 90 and lactate < 2 mmol/L; $n = 90$) had a lower in-hospital mortality of 9% as opposed to a 26% in-hospital mortality ($p < 0.02$) in those with tissue dysoxic shock (SBP < 90 and lactate > 2 mmol/L; $n = 157$).¹⁰¹

- *Cryptic shock in congestive heart failure (CHF).* In another study, patients with end-stage CHF with an ejection fraction of $\leq 30\%$ presenting in decompensated CHF were stratified by lactate levels. They were then treated by protocol using ScvO₂ as a real-time guide to management instead of traditional use of vital signs alone. The treatment group was compared with a control group of clinic patients with known, stable, end-stage CHF (EF $< 30\%$) for 3 months. There was *no statistical difference in vital signs* or Killip and New York Heart Association criteria among the three groups. The authors found that 50% of their patient population with normal vital signs (as designated by the control group) had evidence of ongoing biochemical shock with significantly lower presenting ScvO₂ and higher lactate. Both values significantly improved with protocol-directed treatment based on ScvO₂ and lactate rather than vital signs alone.^{50,51}
- *Cryptic shock in general shock patients.* Rady and Rivers evaluated patients presenting to the ED in shock. After triage, the patients were resuscitated to a MAP > 70 mm Hg and CVP ≥ 15 mm Hg. After achieving MAP and CVP goals, ScvO₂ and lactate were measured. They found 50% of patients with a MAP > 70 mm Hg and SBP > 100 mm Hg had a ScvO₂ $< 65\%$ and a lactate

level > 2 . This level of anaerobic metabolism supported a continued process of biochemical shock in the face of traditionally “normal” blood pressure. Additional resuscitation led to a significant increase of ScvO_2 (52–65%; $P < .05$) and decreased lactate (4.6–2.6; $P < .005$) while MAP and SBP remained unchanged.⁵³

- *Cryptic shock in trauma patients.* “The Golden Hour and Silver Day”⁴⁵: Occult shock in trauma patients has been extensively studied. Scalea et al. demonstrated that biochemical markers of hypoxia were present in trauma patients with “normal” vital signs. Thirty-nine percent of patients with normal vital signs had evidence of tissue hypoxia ($\text{ScvO}_2 < 65\%$, lactate > 2.5 mmol/dL). The occult hypoxia group had more extensive injuries and greater blood loss, and they required significantly more transfusions.⁴³ Another study evaluated lactate clearance in critically injured trauma patients who had an elevated lactate, SBP > 100 , pulse rate < 120 , and urine output > 1 mL/kg/h. Sixty-eight percent of patients had occult hypoperfusion (elevated lactate with normal blood pressure) during the first 24 hours. Of those with occult hypoperfusion, if the lactate was cleared within 24 hours, multisystem organ failure, respiratory compromise, and mortality were significantly reduced ($P < .05$). The authors concluded that early identification and aggressive resuscitation based on biomarker normalization improved survival and reduced morbidity in the critically injured patient.⁴⁵ Other studies have since confirmed the concept of resuscitation to normalization of biomarkers in trauma patients.^{102–105}

DISPOSITION

As soon as a shock patient is identified, the ICU should be notified and admission or transfer should be initiated. However, due to stressed ICU resources, the critically ill or injured patient may reside in the ED longer than optimal or appropriate. The emergency physician should have a clear understanding of the care required, balanced with the resources available for optimal patient care and disposition.

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Pediatric Considerations

Fernando L. Soto • Ariel E. Vera

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INTRODUCTION

Pediatric visits account for 20–25% of visits to emergency departments in the United States. Most of these encounters will occur in general emergency departments, which may have limited capabilities to care for the critically ill child.^{1–3} The priorities in the assessment and management of the pediatric patient are similar to those of the adult patient. The quoted ABCs of airway, breathing, and circulation still apply and are first and foremost in the evaluation of the young infant and child. However, there are certain anatomic, physiologic, developmental, and social considerations that are unique to this population and that must be taken into account during the evaluation and treatment. This chapter will focus on the key differences in the treatment of the critically ill child. A complete discussion of the many procedures, and the presentation of every critical condition in pediatric patients, is well outside the scope of this text. See Table 62-1 for a list of medications used in pediatric resuscitation.

AIRWAY

Recognition of Respiratory Distress

Compared to adults, infants and children have anatomic and physiologic characteristics that make them more susceptible to respiratory emergencies. During the first 6 months of life, they are obligate nose breathers, and their narrow nasal passages tend to increase resistance to flow and can easily become occluded with a simple upper respiratory illness that will

lead to obstruction. Following Poiseuille's law of resistance in which resistance is inversely proportional to the radius to the power of four ($R \propto 1/r^4$), small changes in the radius (mucosal edema, debris, etc.) will cause great increases in resistance. Infants and children have weak abdominal muscles and diaphragm, which may tire easily if strained. In addition, they have faster metabolic rates, which require a higher oxygen demand. This higher oxygen demand, coupled with a decreased functional residual capacity, makes them more vulnerable to decreases in their oxygen levels compared with those of adults.⁴ That children tend to have higher respiratory rates, even at rest, is based on these differences.

One must be familiar with the normal vital signs according to the age (see Table 62-2) of the child. Signs of distress may be subtle. For example, in neonates, sometimes the only complaint may be distress during feedings or decreased intake, which should prompt the examiner to further investigate the etiology. Associated fatigue, bluish skin discoloration, or sweating while feeding and weight changes will prompt the examiner to think of congestive heart failure, dysrhythmias, or hereditary conditions such as cystic fibrosis.^{5–7}

The child's general appearance is the best guide to the level of distress. Patients with mild tachypnea who smile or feed without difficulty and are able to track the examiner (maintain eye contact) are likely not in extremis. Close attention should be directed to those who look ill and appear irritable or lethargic. See Table 62-3 for a list of findings in the respiratory-distressed child.

Failure to adequately manage the airway is a leading cause of preventable deaths in the pediatric population.


TABLE 62-1: Common Medications Used in Pediatric Resuscitation

Epinephrine	0.01 mg/kg (0.1 mL/kg) IV every 3–5 min (1:10,000) in active resuscitation
Atropine	0.02 mg/kg IV every 5 min (minimum dose 0.1 mg, maximum dose 1.0 mg)
Adenosine	0.1 mg/kg IV (maximum dose 6 mg). May double to 0.2 (maximum dose 12 mg)
Amiodarone	5 mg/kg bolus for pulseless VT and over 20–60 min if perfusing arrhythmia—expert consultation advised
Narcan	0.1 mg/kg/dose IM/ET/IV/IO every 2–3 min (maximum dose 2 mg/dose)
Glucose	5–10 mL/kg of D10W in neonates and infants 2–4 mL/kg of D25W in young children 1–2 mL/kg of D50W in older children and adults
Calcium	100 mg/kg 10% calcium gluconate or 20 mg/kg of 10% calcium chloride
Lidocaine	1 mg/kg IV, and then infusion
Bicarbonate	1 mEq/kg, may repeat every 10 min
Prostaglandin E1	Start at 0.5 µg/kg/min IV (at lowest effective dose)

Unlike adults, in whom cardiac failure is the primary cause of cardiopulmonary arrest, acute respiratory failure is responsible for most cardiopulmonary arrests in children. Tachypnea is present in all but the most severe respiratory arrests, which may present in apnea with no air movement at all. Many illnesses can initially present with tachypnea, including sepsis, diabetic ketoacidosis (DKA), and abdominal pain.^{4–7} See Table 62-4 for the anatomic and physiologic


TABLE 62-2: Approximate Normal Vital Signs of Pediatric Patients by Age

Age Group	Respiratory Rate (breaths/min)	Heart Rate (beats/min)	Systolic BP (mm Hg)
< 1 month	30–60	90–160	60 ± 10
1–12 months	24–30	110–180	89 ± 25
1–2 years	20–24	90–150	96 ± 30
2–4 years	20–24	75–135	99 ± 25
4–6 years	20–24	60–130	100 ± 20
6–8 years	12–20	60–120	105 ± 13
8–10 years	12–20	60–120	110 ± 15
10–12 years	12–20	60–120	112 ± 15
12–14 years	12–20	60–120	115 ± 20
14 to adult	10–16	60–120	120 ± 20

Formulas that may help treating infants and young children:
Blood pressure estimate:

$$70 + (2 \times \text{age}) = 50\text{th percentile}$$

$$90 + (2 \times \text{age}) = 90\text{th percentile}$$

Estimated body weight (kg) = $2 \times (\text{age in years}) + 8$ or $(9 + \text{age in months})/2$
A patient should double birth weight by 6 months, and then triple it by 1 year of age (estimated weight in a 1-year-old ~10 kg).


TABLE 62-3: Signs and Symptoms in the Child with Respiratory Distress

Finding	Comment
Grunting	Increases auto-PEEP; maintains functional residual capacity
Tripod position	Improves or relieves airway obstruction
Retractions	Supraclavicular or abdominal
Stridor	Consider upper airway obstruction
Apneic spells	Impending respiratory arrest in infants
Coughing	Expiratory mechanism in bronchospasm or obstruction
Head bobbing	Neck muscles used to increase inspiratory pressure
Nasal flaring	Decreases airway resistance

PEEP, positive end-expiratory pressure.

Data from Santillanes G, Gausche-Hill M. Pediatric airway management, *Emerg Med Clin North Am* 2008 Nov;26(4):961–75.

differences in the pediatric airways and recommended treatment strategies.

Oxygen Administration

Pediatric patients have a very small tolerance for hypoxia. Young infants may benefit from blow-by oxygen by cupping the hand or small nasal cannulas. Cannulas have the advantage of providing oxygen while creating a small amount of positive end-expiratory pressure (PEEP); both of these methods stimulate the infant while preventing apneic spells. The best way to deliver close to 100% oxygen is with a face mask with a reservoir such as a non-rebreather mask. This may be uncomfortable to very young children, so considering the use of alternative methods is recommended.^{5,8,9} Heated, humidified high-flow nasal cannula (HFNC) is a modality that has gained popularity in intensive care units. It provides oxygenation at pressures approaching continuous positive airway pressure (CPAP). Although studies are limited, recent literature has shown it to be associated with decreased rates of intubation in pediatric patients with respiratory distress in the emergency department.¹⁰

Medications

Next to oxygen, the most important pharmacologic intervention to consider in respiratory failure is epinephrine. At low doses, it is primarily a β -receptor agonist causing strong bronchodilation, decreasing mucosal edema, and improving cardiovascular status with a very short onset of action. It may be administered intramuscularly or intravenously for anaphylaxis, asthma, severe croup, or upper airway edema, among other conditions. For respiratory distress, upper airway obstruction, or edema, it can be given in nebulized form. The standard dose is racemic epinephrine 0.5 mL of the 2.25% concentration. “Crash cart” epinephrine (1:1,000) may also be used by administering 3–5 mL in a nebulizer.¹¹



TABLE 62-4: Structural Differences in the Pediatric Airway Versus Adult Airway

Anatomy	Effect	Intervention
Larger occiput relative to body	Promotes passive flexion of cervical spine leading to airway obstruction	Maintain sniffing position; avoid hyperextension. Rolled towel under shoulder may assist ventilation and intubation
Smaller airway	More susceptible to airway obstruction from edema, mucous plugs, or foreign bodies	Oral and nasal inspection and suctioning
Larynx higher and more anterior	Difficult to visualize the vocal cords during intubation	Cricoid pressure can facilitate intubation
Narrowest portion of trachea at level of the cricoid ring	Dictates size of ETT	Use cuffed ETT in children older than 8 years of age Use cuffed or 0.5–1.0 size smaller uncuffed ETT in younger patients
Short trachea	Intubation of right mainstem bronchus more likely	Vigilance with depth of ETT insertion (formula: $3 \times \text{ETT size at lip}$)
Relatively large tongue and a floppy epiglottis	Tongue can fall back against the posterior pharynx with loss of tone, deep sedation, or CNS dysfunction	Chin lift Jaw thrust in suspected cervical spine injury Use oral airway only in unconscious patients May use nasal airway in conscious patients but avoid in suspected basilar skull fractures, CSF leaks, or coagulopathy

ETT, endotracheal tube; CNS, central nervous system; CSF, cerebrospinal fluid.

BREATHING

Ventilation

When the previous interventions are not enough to maintain adequate ventilation, assistance may be required. Respiratory failure is defined as hypoxemia (arterial $\text{Po}_2 < 60$ mm Hg) and hypercarbia (arterial $\text{Pco}_2 > 55$ mm Hg) with associated respiratory acidosis. However, intubation is considered a clinical decision and should not be withheld while awaiting any laboratory testing.⁴ Signs of impending respiratory failure include altered sensorium or deterioration in mentation, progressive hypoxemia, severe work of breathing, silent chest, or apnea. For a complete list, please refer to Table 62-5. Recent use of new noninvasive tools can also help with assessment of ventilatory status. End-tidal CO_2 (ET CO_2) monitors are a widely available yet underutilized.¹² ET CO_2 levels can correlate with blood gas pCO_2 in pediatric patients with moderate to severe respiratory distress.¹³

The ability to provide proper bag-valve ventilation is a vital skill in the airway management of adult and pediatric patients. In the prehospital setting, studies have shown that

bag ventilation may be as beneficial, if not more so, as endotracheal intubation.^{5,14,15} Ventilations may be provided for a prolonged amount of time with the goal of chest elevation and with care not to overinflate the stomach. Increasing pressure in the stomach will increase the likelihood of vomiting and therefore the risk for aspiration, as well as impairing ventilation by increasing intra-abdominal pressure. Adding a nasogastric tube whenever prolonged bagged ventilation is anticipated may decrease the occurrence of these complications.

Noninvasive Positive Pressure Ventilation (NIPPV)

NIPPV is preferred initially in carefully selected groups of patients in order to treat their hypoxemia while reversing the disease process in attempt to avoid endotracheal intubation (see chapter 7 on Noninvasive Ventilation). In pediatric patients, there are different options available to improve ventilation and decrease the risk of intubation. As previously discussed, HFNC may improve ventilation while providing some PEEP. Most studies for pediatric applications of NIPPV have been done in neonates.^{16,17} In these studies, patients are usually placed on a continuous NIPPV, HFNC, or CPAP modes.^{10,16–19} Recent work has shown that bilevel positive airway pressure (BiPAP) mode may have faster resolution of symptoms, is better tolerated, and has fewer side effects. Finally, “bubble CPAP” can be done by placing the expiratory limb of the breathing circuit under water. This provides, in addition to the CPAP, a high-frequency ventilation effect, producing small vibrations in the infant’s chest at the frequency of 15–30 Hz. This modality, when used in neonates, may contribute to gas exchange, thus reducing the work of breathing.²⁰ All therapies may be utilized in multiple respiratory conditions such as asthma, bronchiolitis, pneumonia, and the like.^{21,22} In infants and older children, the



TABLE 62-5: Indications for Endotracheal Intubation

- Cardiac arrest (or impending arrest)
- Severe respiratory distress as evidenced by accessory muscle use and fatigue, nasal flaring, altered mentation, grunting, silent chest, bradypnea, etc.
- Unsuccessful airway management with bag–valve mask ventilation
- Hypoxemia ($\text{Po}_2 < 50$ mm Hg), hypercarbia ($\text{Pco}_2 > 55$ mm Hg)
- Coma or absent gag reflex
- Severe trauma or shock

use of bubble CPAP is less established. Similar indications and contraindications apply to use with children than with adults. Patients who could benefit from this modality must be conscious, have a protected airway with an intact gag reflex, and be able to breathe spontaneously. Contraindications to this therapy are facial injuries, impending respiratory failure, altered mental status, or inability to maintain the airway.¹⁷⁻²⁰

Some patients may require sedation for optimal management. Ketamine has been established as the sedative of choice. Ketamine does not affect the airway, maintains an intact airway, and has bronchodilator effects, and its safety record makes it the best choice for this particular procedure.^{19,23} Benzodiazepines are not recommended due to their effects on respiratory depression in an already compromised patient.

Initial setting recommendations for each mode are 2–3 L/min (lpm) in HFNC and 5 lpm for bubble CPAP. In older children, consider CPAP with initial recommended setting at 10–14 cm H₂O. For BiPAP, the initial recommended settings are an inspiratory pressure of 12–15 cm H₂O and an expiratory pressure of 6–7 cm H₂O.

Invasive Positive Pressure Ventilation

Definitive airway management entails endotracheal intubation and mechanical ventilation. In the presence of severe trauma, altered mental status leading to coma, organ failure, or respiratory depression, a definitive airway should be considered. There are some crucial differences in ventilation between children and adults. Even if you are familiar with ventilation, consulting an expert in pediatric intensive care is highly recommended whenever you reach this point.

Intubation

The most important considerations for a successful intubation are evaluation of the airway, anticipating complications, and having the necessary equipment. If time permits and the required equipment or staff are unavailable, assist ventilation using bag-valve ventilation until the equipment is verified and prepared (a more extensive discussion in chapter 1 [approach to difficult airway] and in chapter 2 [physiology of the peri-intubation]).

Rapid sequence intubation (RSI) has become the cornerstone in emergency airway management. Since its advent, outcomes in emergent endotracheal intubations of children and adults have improved greatly. Careful attention should be directed to the patient with a potentially difficult airway. The anatomic and physiologic differences in the pediatric patient dictate for adjustments in RSI preparation and execution. Most of the commonly used medications for RSI in adults are also used in pediatric patients, but some drugs are used more frequently in children. For premedication, atropine can be administered prior to intubation to blunt vasovagal hypotension and to reduce the prevalence of arrhythmias that can occur during laryngoscopy in pediatric patients.²⁴ For sedation purposes, ketamine is well studied in the pediatric population, and it is safe in patients with hypotension



TABLE 62-6: List of Rapid Sequence Intubation (RSI) Medications

Atropine	0.02 mg/kg (min 0.1 mg, max 1.0 mg) IV, IM
Lidocaine	1 mg/kg (max dose 100 mg) IV
Thiopental	3–5 mg/kg (max dose 25–75 mg) IV
Ketamine	1–2 mg/kg IV or 3–4 mg/kg IM
Etomidate	0.3 mg/kg IV
Midazolam	0.1–0.2 mg/kg IV, IM
Propofol	2.5 mg/kg (max dose 20 mg/bolus) IV
Succinylcholine	1–2 mg/kg (max 100 mg) IV, IM
Rocuronium	0.6–1 mg/kg IV
Vecuronium	0.1–0.2 mg/kg IV

or shock. It is also recommended in patients with respiratory conditions such as asthma since it induces bronchodilation (see Table 62-6 for a list of RSI medications).²³ A more extensive discussion in chapter 1 (approach to difficult airway) and in chapter 2 (physiology of the peri-intubation).

For intubating pediatric patients, the Miller (straight) blade is generally preferred since it can displace the large, floppy epiglottis and may help reach the pediatric vocal chords, which will be superior and anterior. The Macintosh (curved) blade may also be used according to the level of the practitioner's expertise and level of comfort.^{4,9}

Endotracheal tubes (ETTs) come in different shapes and sizes. Of the many ways to calculate the size of the ETT, the quickest way to estimate the size is by using the patient's pinky. This digit should be as large as the airway, plus or minus a few millimeters. On the other hand, applying the formula of adding 4 to the patient's age divided by 4 ($[\text{age} + 4]/4$) gives an approximation of the tube size. Multiplying the ETT size by 3 gives an approximation of the number where the tube should rest against the lip commissure. For example, a 4-0 ETT should be introduced with the 12-cm mark at the lip. Recent recommendations state that cuffed tubes should be used in children older than 8 years of age, while both types (cuffed or uncuffed) may be safely used in younger children and infants, except newborns. Caution must be taken to maintain cuff pressures well under 20 cm H₂O to avoid mucosal ischemia in the subglottic region. Under certain conditions such as increased lung resistance, cuffed tubes may be preferred.⁴

The most reliable approach in a pediatric emergency situation is to use a length-based resuscitation system such as the commercial Broselow-Luten™ tape with color-coordinated code cart shelves. These can be used in children 12 years or younger and give information on ETT sizes, blade numbers, indwelling catheters, and medication dosages based on the patient's ideal weight. Although there is some controversy regarding whether the tapes accurately measure the patient's weight, it is still useful and safest to utilize this guide.²⁵ It is also important to remember that these are only guidelines and that ETTs a half-size larger or smaller should be ready and available if there is any complication or inability to intubate.

As with adults, other approaches to pediatric airways must be considered. More evidence of the use of these adjunct

treatment strategies is being published, and practitioners should have access to video-assisted laryngoscopy, supraglottic devices, and surgical airways as options to a failed airway, and these should be included in treatment algorithms in your institutions if possible.^{26,27}

Mechanical Ventilation

Mechanical ventilators have a multitude of settings that go beyond the scope of this chapter and will be discussed elsewhere in this textbook. Generally speaking, for infants and neonates younger than 1 year or weighing < 10 kg, the ventilator is usually set in pressure-limited cycles since most ventilators cannot deliver restricted low tidal volumes as small as 40–60 mL. Pressure cycles also decrease the rate of barotrauma and ventilator-induced lung injury (VILI). The downside of this modality is that tidal volumes (V_t) are variable and not guaranteed, with potential for hypoxemia. In situations with decreased lung compliance, a decrease in the V_t reaching the lungs is seen, whereas, in situations with increased compliance, the V_t will exceed the expected. To begin ventilation with this modality, pick either synchronized intermittent mandatory ventilation (SIMV) or assist control (AC) mode. The trigger will be pressure, so set positive inspiratory pressure (PIP) between 15 and 20 cm H₂O and titrate up just enough to get an adequate chest rise. Set the PEEP at 3–5 cm H₂O. Maintaining oxygen saturation > 92% should guarantee appropriate oxygenation. In older children and adults, volume cycles seem to be the preferred mode; the ventilator will deliver a set V_t regardless of the pressure necessary to achieve that delivery. See Table 62-7 for initial ventilation settings in pediatric patients. Something to remember: there are very limited evidence-based data on specific modalities. It is important to note that choice of modality is user-driven, and users should use the mode they feel most comfortable with while maximizing patient benefit. Avoid unnecessarily high levels of oxygen by keeping the fraction of inspired oxygen (FiO₂) at the lowest level to maintain adequate oxygenation to avoid oxygen toxicity. There is a higher correlation of oxygen toxicity and FiO₂ > 70, so it is reasonable to titrate the FiO₂ using O₂ saturation or the arterial blood gases (ABG). The goal should be to ventilate and oxygenate with minimal lung damage. In the advent of acute respiratory

distress syndrome or to prevent it, lung-protective ventilation is recommended using V_t 4–6 mL/kg in conjunction with a higher respiratory rate to achieve an adequate minute ventilation, limiting plateau pressure to < 30 cm H₂O. Hypercapnia is expected, and the term *permissive hypercapnia* is tolerated as long the arterial pH is kept > 7.20. A trial in adults and pediatric populations showed a significant decrease in mortality.²⁸ Pediatric patients who have worsening hypoxemia should be referred early for extracorporeal membrane oxygenation (ECMO) (see chapter 9 on ECMO).

CIRCULATION

Shock is a state of inadequate tissue perfusion of oxygen and nutrients leading to abnormal cellular function. Pediatric patients respond differently to shock than do adults. The first and most sensitive response to shock in a pediatric patient is tachycardia; the underdeveloped myocardium prevents them from modifying their stroke volume (SV) as needed. Based on the formula $CO = SV \times HR$, in which CO is cardiac output and HR is the heart rate, the only way pediatric patients can increase their CO is by increasing heart rate. If an adult faces a need for increased blood flow, doubling the resting heart rate from 70 to 140 will more than double the CO. On the other hand, infants and children have, at baseline, higher resting heart rates, and doubling the resting heart rate from 150 to 300 would not be as effective due to shortening diastolic times leading to decreased coronary artery perfusion and cardiac preload time. It is important to note that, in children, blood pressure in itself should not be used to monitor severity of illness or response to treatment.²⁹ Young patients have a very strong response to a decrease in effective circulatory volume. They have lower baseline blood pressures and are able to increase their systemic vascular resistance significantly to compensate. This benefit, at the same time, gives the examiner a false sense of security since hypotension may be a late finding in an already decompensated child. Prompt recognition and reversal of shock is warranted to avoid morbidity and mortality (see chapter 61 on shock).^{29–33}

Acute phase reactants are advocated as part of the evaluation of a child in shock. However, examination of the child will provide much of the needed information regarding the severity of the shock and dehydration status, thus circumventing



TABLE 62-7: Initial Settings on for Pediatric Patients on Mechanical Ventilation

Parameter	Infants (< 10 kg) or those with decreased compliance	Older children and adults
Modality	Pressure-controlled	Volume-controlled: assist control (AC) or SIMV
Settings	Positive inspiratory pressure (PIP) 15–20 cm H ₂ O (minimal required for adequate chest rise)	Tidal volume: 5–8 mL/kg
Respiratory rate	30–40 breaths/min	Adequate for age (12–20 breaths/min)
FiO ₂	Begin at 100% and decrease to lowest possible required for adequate O ₂ saturation near 99%	
I:E ratio/IT	Inspiratory:expiratory ratio of 1:2 or inspiratory time of 0.5 s (may be modified as per special requirements [e.g., air trapping])	
PEEP	3–5 cm H ₂ O higher if poor lung compliance (i.e., ARDS) or none at all if air trapping present (i.e., asthma)	

the need to wait for lab results prior to instituting treatment. The most useful findings for $> 5\%$ dehydration are prolonged capillary refill time, abnormal skin turgor, and abnormal respiratory pattern. Other useful findings include a blood urea nitrogen (BUN) > 45 mg/dL (LR 46.1 [2.9–73.3]) and bicarbonate level > 17 mEq/L (LR 3.5 [2.1–5.8]).³⁴ To further categorize the severity of dehydration and shock, the ultrasound proves to be invaluable. Although controversial, recent studies have shown that assessing the inferior vena cava index can be used to evaluate and monitor level of dehydration and provide the practitioner with an approximation to the patient's intravascular status.³⁵

Treating Shock

In non-critical patients, consideration should always be given to oral rehydration therapy (ORT), with or without aid from antiemetic medications. For every 25 children treated with ORT one would fail and require intravenous hydration.³⁶ Other options would include rehydration through a nasogastric tube and subcutaneous rehydration with the use of hyaluronidase.^{37,38}

For critically ill patients, other more aggressive interventions will be warranted. Intravenous or intraosseous (IO) access is vital in the treatment of any kind of shock. Placement of two peripheral lines is usually more than enough, but in cases of severe shock and dehydration, this may prove difficult. Classic teaching states that in the critically ill child, inability to gain vascular access within three attempts or 90 seconds should prompt placement of an IO line. Newer systems make this process easier, and anticipating a difficult line may be more than enough.^{5,9} Through an IO, fluids and resuscitation drugs may be administered easily.³⁹ For a more definite access, inserting a central line using the Seldinger technique will also provide the ability to get blood for sampling. In children and infants, the preferred approach is the femoral and external jugular veins, but this approach is not needed for the immediate initial stabilization of pediatric patients in an emergency department with IO access available.^{5,9,38–40}

Categorizing Shock

The many etiologies responsible for shock can be categorized based on the type of dysfunction present. Shock may be cardiogenic, hemorrhagic, neurogenic, obstructive, dissociative, or distributive in nature. See Table 62-8 for shock etiologies and their treatment.

Worldwide, the most common cause of shock is hypovolemia secondary to vomiting and/or diarrhea. It also can ensue from bleeding or dehydration with associated electrolytic disturbances. Other common causes include burns, trauma, and metabolic disorders such as diabetic ketoacidosis (DKA). Treatment includes isotonic volume expansion followed by blood transfusion in the trauma setting. Comparatively, children may require more fluids per kilogram of weight, but close monitoring is of paramount importance. In the presence

of shock, the initial bolus is 20 mL/kg over 5 to 10 minutes followed by reassessment of vital signs and mental status. Studies have shown similar outcomes whenever crystalloids or colloids are used as long as resuscitation is adequate.^{40–42} In the trauma setting, blood is administered at 10 mL/kg aliquots after initial expansion of 40 mL/kg of normal saline or Ringer's lactate. Younger infants and children with cardiac or renal conditions should receive smaller boluses of 10 mL/kg with close monitoring to avoid fluid overload (see chapter 38 on blood products).

Septic Shock

Sepsis in the pediatric population deserves further discussion among other shock etiologies. One of the most common pediatric complaints in the ED is fever, and children commonly present with tachycardia and vasodilation as well. It should be emphasized that the vast majority of these children will have self-limited illnesses and will do well. However, in severe sepsis and septic shock, additional findings will include hyper- or hypothermia, ill appearance, changes in mental status, oliguria, prolonged capillary refill (CR) of > 2 seconds in cold shock, and peripheral vasodilation in warm shock. Hypotension with bounding pulses is considered warm shock; diminished peripheral perfusion with prolonged CR is considered compensated cold shock, whereas hypotension with associated prolonged CR is considered decompensated shock. As previously stated, hypotension is not a requirement for the diagnosis of septic shock since pediatric patients are able to maintain their blood pressure effectively despite deterioration.

Another crucial difference is that pediatric patients will require proportionally more fluid in resuscitation due to their usual hypovolemic state in sepsis and will require earlier intubation strategies due to their low functional residual capacity.^{27,30,32}

Early recognition and use of resuscitation protocols as recommended by the Society of Critical Care Medicine have shown to decrease mortality to approximately 2% in previously healthy children and 10% in chronically ill children, with a number needed to treat of 3.3.³² In a study by Han et al., approximately 3% of pediatric transports to a pediatric emergency department had a final diagnosis of septic shock with a mortality approaching 25%.³¹

Treatment

The main goal of treatment in pediatric septic shock is early recognition, followed by aggressive fluid resuscitation with early administration of antibiotics. Manage the airway and get vascular access, as previously discussed. Approximately 40% of CO is dedicated to the work of breathing. Intubating and sedating the patient will allow the CO to be dedicated to vital organs. Administer an initial fluid bolus of 20 mL/kg of normal saline or 5% albumin over 5–10 minutes and repeat if there is no improvement. These patients may require close to 60 mL/kg or more in certain situations. Reassess after each



TABLE 62-8: Different Types of Shock in Children and Their Treatment

Type/Clinical Scenario	Pathophysiology	Signs and Symptoms	Treatment
Hypovolemic Most common cause is vomiting and diarrhea. May be seen in any type of bleeding or TS (nephrotic syndrome, pancreatitis, burns, etc.)	↓ CO ↑ SVR IV and Int losses	↑ HR ↓ BP ↑ RR Prolonged CR Dry skin Oliguria AMS	Initial 20 mL/kg bolus × 1–2 If hemorrhagic, provide pRBCs at 10 mL/kg after second bolus Look for site of blood loss (abdomen, open wounds, large bone fractures, etc.) Administer 10 mL/kg of NSS in cases of DKA, cerebral edema, or fluid overload (e.g., renal failure, CHF, etc.)
Septic Acutely ill with suspicion or evident source of infection Three main mechanisms	↑ CO, ↓ SVR (20%) ↓ CO, ↑ SVR (60%) ↓ CO ↓ SVR (20%)	↑ HR, ↓ BP, ↑ RR, AMS, bounding pulses, flushing, TS, edema ↑ HR, normal or ↓ BP, ↑ RR, AMS, ↓ pulses, delayed CR, TS, edema ↑ HR, ↓ BP, ↑ RR, AMS, ↓ pulses, delayed CR, TS, edema	Repeat 20 mL/kg bolus; may need > 60 mL/kg in first hour (up to 200 mL/kg in some cases). ¹⁸ Consider colloids Add inotropics as per protocol. Dopamine is first choice Consider epinephrine (cold shock) or norepinephrine (warm shock) Treat hypoglycemia/hyperglycemia and hypocalcemia, and protect from hypothermia Consider steroids for catecholamine-resistant shock.
Distributive Anaphylaxis: Hx allergy and/or exposure to allergen, vomiting, rash, flushing, etc.	↑ CO, ↓ SVR	Angioedema, rapid TS, ↓ BP, respiratory distress	Start with epinephrine, steroids, and antihistamines. May require continuous epinephrine infusion
Spinal cord injury: Patients present after contusion/ transection of cervical spine (T6 or above) sympathetic loss with unopposed vagal tone	Normal CO, ↓ SVR	↓ BP, with normal to ↓ HR, paralysis with loss of vascular tone	Aggressive fluid therapy Pharmacologic support of SVR with vasopressors: norepinephrine or phenylephrine Evaluate and treat associated injuries
Cardiogenic History evident for congenital heart disease, myocarditis, dysrhythmias, etc.	↓ CO, normal to ↑ SVR	Normal to ↑ HR, ↓ pulses, delayed CR, oliguria, JVD, hepatomegaly BP normal until late in course	Pharmacologic support of CO with dobutamine, milrinone, and dopamine Judicious fluid replacement as indicated clinically. Prostaglandin E1 in cases of ductal dependent lesions

CO, cardiac output; SVR, systemic vascular resistance; HR, heart rate; RR, respiratory rate; CR, capillary refill; BP, blood pressure; AMS, altered mental status; TS, third spacing; Hx, history; NSS, normal saline solution; IV and Int losses, intravascular and interstitial losses; JVD, jugular vein distension; CHF, congestive heart failure. *Note:* Signs and symptoms are not in order of progression and some may not be observed at all (i.e., low BP). *Pediatric patients will have normal BP until late in the course.*

bolus. Palpable hepatomegaly or rales on lung examination will be found in fluid overload. If signs of fluid overload are present, boluses should be of only 10 mL/kg aliquots and careful monitoring should take place. Diuretics, peritoneal dialysis, and continuous renal replacement therapy may be

considered in patients who have undergone stabilization but are unable to manage the fluid overload.²⁹

Inotropic agents should be added to patients who present with fluid-resistant shock (Table 62-9). Fluid-refractory shock is the presence of clinical signs of shock after 60 mL/kg



TABLE 62-9: Vasopressor Therapy

Inotropic Agent	Effect	Dosing (μg/kg/min)	Recommendation
Dopamine	Dopaminergic β-Adrenergic α-Adrenergic	1–5 5–15 > 15	Initial treatment of septic shock unresponsive to initial fluids, during initial resuscitation. Particularly useful when ↓ CO + ↓ SVR
Norepinephrine	α, β	0.01–0.3	If unresponsive to dopamine infusion in the presence of warm shock
Epinephrine	β, α (higher doses)	0.01–0.3	(norepinephrine) or cold shock (epinephrine)
Dobutamine	β	5–15	Use with dopamine for initial treatment of hyperdynamic or “cold” shock (↑ SVR and ↓ CO)

SVR, systemic vascular resistance; CO, cardiac output.

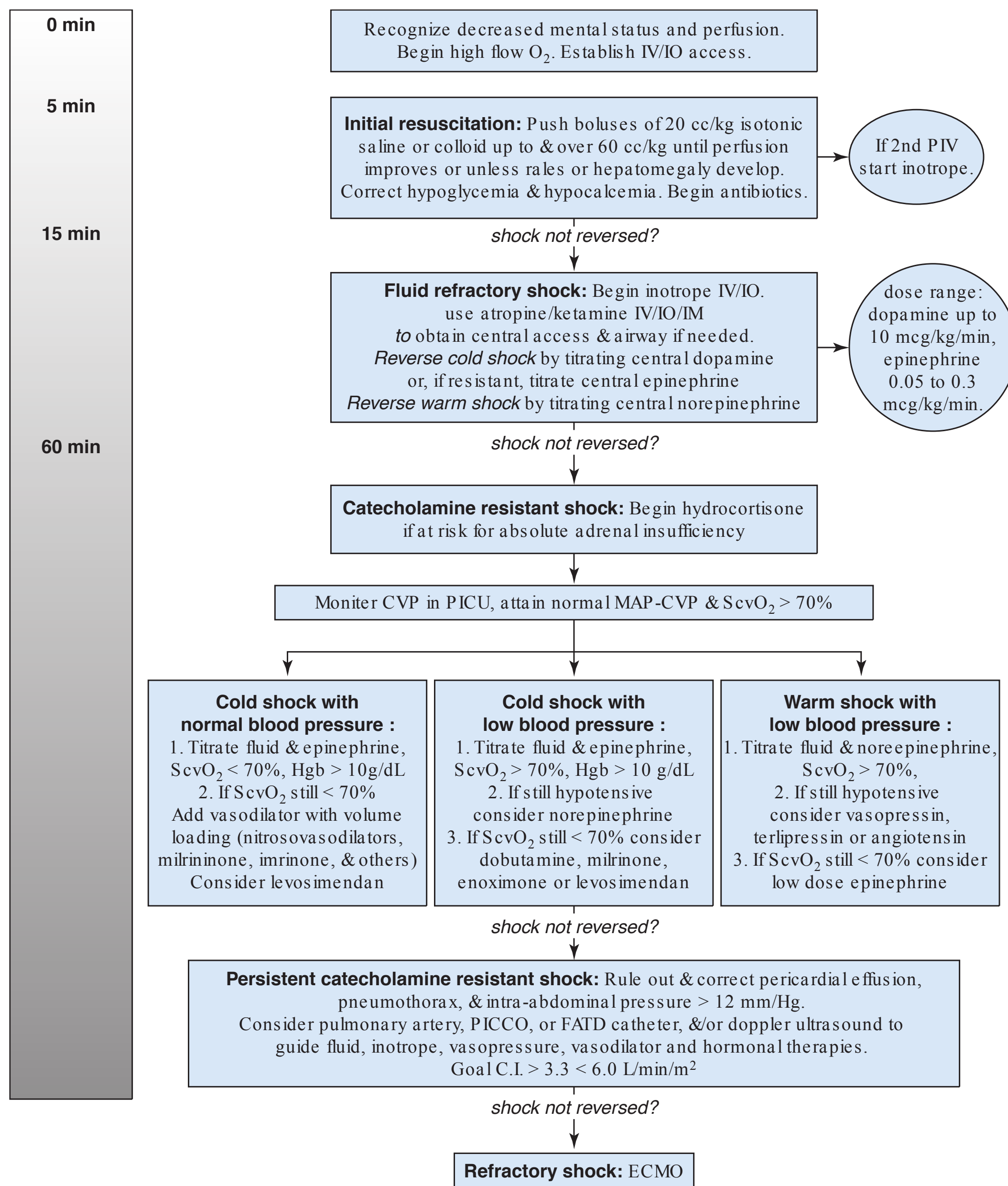


FIGURE 62-1 Approach to management of pediatric septic shock. (Reproduced with permission from Brierley J, Carcillo JA, Choong K, et al: Clinical practice parameters for hemodynamic support of pediatric and neonatal septic shock: 2007 update from the American College of Critical Care Medicine, *Crit Care Med.* 2009 Feb;37(2):666–688.)

of fluid administration. In most patients, dopamine remains the first-line agent for fluid-refractory shock, although some studies suggest that infants younger than 6 months may not have enough norepinephrine stores due to an immature sympathetic innervation. Adding dobutamine to this initial intervention will be beneficial. In the presence of dopamine-resistant shock, titrating epinephrine (cold shock) or norepinephrine (warm shock) is beneficial in most cases. In the absence of central line access, inotropes should be administered peripherally as long as there is close monitoring of the area for any signs of necrosis. In the presence of cate-

cholamine, dexamethasone at a dose of 1–2 mg/kg may be administered in patients at risk for adrenal insufficiency (see Figure 62-1).^{29,30,32,33}

Infants have particularities compared to their older counterparts. Very young infants have low glycogen stores and underdeveloped thermoregulatory systems. Pay close attention to hypothermia and electrolyte disturbances such as hyperglycemia or hypoglycemia and hypocalcemia.

The therapeutic goals of intervention in septic pediatric patients in the emergency department include restoration of capillary refill to < 2 seconds and normal mental status,

pulses, and blood pressure, with an adequate urine output of > 1 mL/kg/h, within 1 hour of arrival.^{29,32,33} Even if the patient improves significantly during the first hour, admission to a pediatric intensive care unit is warranted.

OTHER CONSIDERATIONS

Toxicology

Pediatric patients comprise approximately 62% of annual human exposures,⁴³ and children most commonly ingest medications, cosmetics, and household products. Fortunately, most of the cases are seldom lethal and just require observation. In cases of suspected poisoning, ipecac syrup and gastric lavage are no longer recommended. Multiple-dose activated charcoal can be used in children with intact airways within 1 hour of toxin ingestion,⁴⁴ and whole bowel irrigation can be used if sustained-released or enteric-coated pills are suspected. During initial evaluation, hypoglycemia treatment is essential. Intravenous dosages of glucose solution may be 10 mL/kg of 10% glucose, 4 mL/kg of 25% glucose, and 2 mL/kg of 50% glucose solution for infants, children, and adults, respectively. Further interventions should focus on supportive treatment and antidote use for specific toxins. Early involvement of Poison Control or a toxicologist is recommended.

Blood Transfusions

Critically ill pediatric patients are at greater risk of developing anemia and require blood transfusions.⁴⁵ Although more commonly seen in intensive care units, these patients can arrive with anemia to the ED. Patients younger than 4 months of age have significantly different metabolic demands and cardiac and hematologic systems that are still in development. These patients require special transfusion protocols that are outside the scope of this chapter. In critically ill but stable children older than 4 months of age, a restrictive transfusion strategy with a threshold of 7.0 g/dL of Hgb is recommended. In unstable patients requiring aggressive resuscitation measures, Hgb levels of 10 g/dL are the usual goal.^{30,32,46} Patients with symptomatic anemia are usually transfused 10 mL/kg of RBCs, with an expected increase of approximately 2–3 g/dL of Hgb. Due to the risk of hypervolemia, rate of transfusion is essential in pediatric patients. Transfusions are given at a rate of approximately 2.5–5 mL/kg/hour, or approximately 1 unit of RBC over 2–4 hours.

Family Presence during Resuscitation

Resuscitative interventions, especially those involving pediatric patients, are very stressful for family members as well as for the medical team. The physical presence of family members during active resuscitation was not always routinely practiced. Not all health providers feel comfortable with allowing the presence of relatives, and the situation must be evaluated on a case-by-case basis.^{47,48} Most commonly cited concerns are legal issues and the effect of the family members' presence

on medical staff performance. Nonetheless, studies suggest resuscitative measures are not interrupted when a protocol is established, and parents report they would be present again in a similar situation due to perceived emotional benefit.^{49,50} For these reasons, recent guidelines support the presence of family members during resuscitation.⁵

Therapeutic hypothermia

There are approximately 16,000 cases of pediatric cardiac arrest in the United States each year.^{1–3} Therapeutic hypothermia has been shown to improve neurologic outcomes in adult cases of post-cardiac arrests, but studies in pediatric patients are limited. Differences in the pathophysiology of cardiac arrest between adult and pediatric patients make it difficult to extrapolate adult data, and some studies have shown no difference in mortality when hypothermia is applied to pediatric arrests or pediatric traumatic brain injury.^{2,51–53}

Therapeutic hypothermia remains a recommendation for adolescents after a witnessed cardiac arrest and neonates with peripartum asphyxia, but it remains controversial in other pediatric populations. Nevertheless, until more conclusive pediatric data are available, current recommendations state therapeutic hypothermia of 32°C to 34°C may be considered in children who remain comatose after cardiac arrest or adolescents who suffered a sudden, witnessed, out-of-hospital ventricular fibrillation cardiac arrest, as well as in those suffering from peripartum hypoxic brain injuries.^{2,5}

CONCLUSION

Not all interventions that make sense in adults yield the same results in young patients. The differences in pediatric and adult critical care management stem from complex social, developmental, and physiologic interactions. More fluid requirements per kilogram than adults, earlier intubation strategies due to earlier failure, and different pathophysiology for cardiac arrests are just some of the peculiarities to be considered. Knowledge of these differences and adequate preparation are key in improving care for this important population.

KEY POINTS

- Clinical examination will provide much of the needed information to categorize and treat infants and children. Findings such as abnormal vital signs, decreased mental status, decreased urine output, ill appearance, and prolonged capillary refill should lead to immediate, aggressive interventions.
- Give consideration to noninvasive ventilation strategies including HFNC and CPAP early in the course of a respiratory processes.
- Young patients have a high capacity to maintain systemic vascular resistance, which leads to hypotension being an extremely late finding in shock; do not delay treatment.

- Early recognition of shock followed by early administration of fluids, antibiotics, and inotropic therapy (even through a peripheral line) in the septic shock patient will significantly decrease mortality when stabilized within the first hour.

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Transportation of the Critical Care Patient

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INTRODUCTION

Moving a critical patient is a dangerous medical intervention. As with any medical intervention, there are risks and benefits. Over time, the risks have been mitigated by creation of specialized transport teams and equipment. The benefits still revolve around providing specialized treatments and diagnostics not available at every facility.¹ Recent literature has shown that time until definitive treatment is an important consideration. All these factors need to be taken into account by the physician when deciding when and how to transport critical patients.

Transporting critical care patients intrafacility or interfacility has some overlap. When moving a patient inside or outside of your facility, the patient needs to be packaged so that he or she is self-contained. All tubes (Foley, nasogastric, intravenous, and drainage), electronic equipment (monitors and pumps), and oxygen equipment must be secured to the patient or vehicle on which the patient is transported.² Equipment and medication to deal with anticipated changes in the event of failure of life-supporting machines must be carried with the transporting team. While transporting inside a facility might only require a small amount of supplies, the longer a transport is in time or distance, the larger the amount of supplies to carry.

The opinions or assertions contained herein are the private views of the author and are not to be construed as reflecting the views of the Department of the Air Force, the Department of Defense, or the US government.

When transporting a patient between facilities, there is a broad array of specialized teams and equipment necessary. The resources are designed to provide scene response, hospital-to-hospital transfers, or medical repatriation. The transport vehicle, skill of providers, and equipment carried in the vehicle vary depending on the mission. Identifying the most appropriate resource requires understanding of the different types.³ In addition, legal issues based around the Emergency Medical Treatment and Active Labor Act (EMTALA) need to be addressed prior to interfacility transfers.

Trauma was the first disease process to identify the benefits of moving critical patients to facilities that could provide definitive care. More recently, cardiac, stroke, and sepsis care have seen the benefits of getting critical patients to definitive treatment. All of these disease processes have realized the time-dependent need for highly specialized care. In many areas, emergency medical services (EMS) have developed systems to get the patients to the most appropriate facility, but sometimes this is not possible and the patients will have to be transferred from one facility to another.

HISTORY

The use of transportation resources to support the overall care of patients has a long-standing tradition. Organized movement of people with illnesses or injuries to higher levels of care began in the Napoleonic Era.⁴ As with many medical advances, military conflict has provided the impetus for

improvement. During the US Civil War, under the leadership of Joseph Barnes and Jonathan Letterman, the beginnings of field treatment and then transport to a higher level of care were established. The Civil War experience was translated into civilian use in New York City as the first urban system in the United States to adopt this care. World War I and World War II provided many steps forward and some steps backward in the advancement of transportation care.

The next big step forward, the use of helicopters for the movement of the injured, started during the Korean War. Helicopters were used more formally in the Vietnam War. The first civilian helicopter services began in the early 1970s and were hospital-based systems.⁵ These services were staffed with a doctor and a nurse. They started to bring advanced care to the prehospital arena.

In 1966, the National Academy of Science–National Research Council released their report entitled *Accidental Death and Disability: The Neglected Disease of Modern Society*. This report helped Congress pass the Highway Safety Act of 1966, which created the cabinet-level Department of Transportation (DOT). The DOT was given the responsibility for improving EMS. Many advancements have occurred in the care provided by both ground and helicopter EMS.

The almost 10-year-old Institute of Medicine (IOM) report titled *Emergency Medical Services at the Crossroads* made many recommendations to improve the whole EMS system including transport agencies and helicopter services.⁶ Some of the recommendations have been accomplished. Significant movement on the recommendation to extend critical care board certification to all acute care and primary care physicians who have completed an accredited fellowship has been made. In addition, the American Board of Emergency Medicine created a subspecialty certification in EMS on September 23, 2010.

RISK VERSUS BENEFIT

When deciding to transfer a patient, the risks and potential benefits related to the patient's condition must be weighed.

Certain medical conditions benefit from specialized facilities that frequently⁷ take care of the condition. The most common conditions for which higher level of care transfers are initiated include trauma, cardiac injury, burns, acute stroke, spinal trauma, obstetric, and pediatric/neonatal-related issues. The risks are twofold: patient deterioration from their disease process and potential transportation-related injury.

Patient deterioration can be mitigated by appropriate stabilization prior to transfer and by providing specialized care transport teams. Complete stabilization prior to transfer might not be possible and could be the reason the patient is being transferred. Specialized teams are limited and might not be readily available. Weather may hamper the ability of specialized teams to get to the facility and limit the transportation mode to slower possibilities.

The hazards of transportation are not commonly considered but need to be taken into account. Medical transport, both air and ground, includes some of the highest risk ways to travel. The inadequacy of appropriate restraining devices, including those for pediatric patients, has been reported. Recent helicopter crashes have brought the issue of medical helicopter safety under National Traffic Safety Board (NTSB) and Congressional scrutiny.⁸ Helicopter EMS crews had the highest fatality rate of all professions (Figure 63-1). Many variables, including weather conditions and time of day, have impact on the risk.

REGIONAL SYSTEMS

In the United States, certain systems have been established to streamline transfers. These include trauma centers, burn centers, and pediatric centers. Pediatric centers, realizing the need for highly specialized transport resources, have maintained control of the transport services, whereas trauma and burn centers usually leave the transport resource decision up to the transferring facility. New systems are being discussed for critical care, cardiac care, and stroke care.

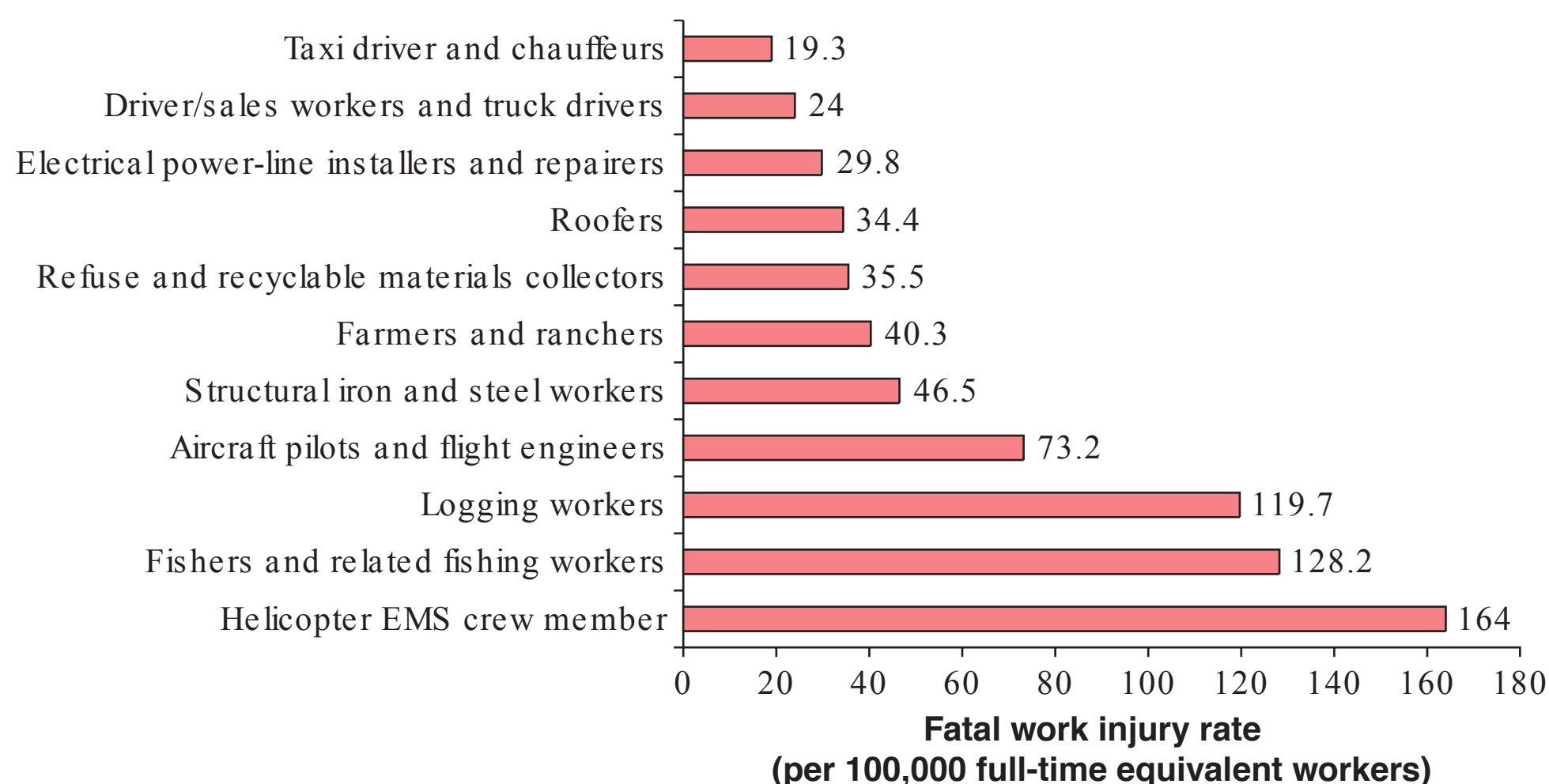


FIGURE 63-1 Selected occupations with high fatal injury rates, 2008.

Trauma systems have been established since the late 1970s to provide a regionalized approach to the care of the traumatically injured patient. The systems are based around limited but highly specialized facilities where increased volume leads to improved outcome. There are more facilities that can provide stabilization and arrange transfer to higher care if needed. Over the 30 years of trauma systems existence, there has been much debate about the need and benefit of helicopter transportation.^{5,9–13} Many studies have shown a survival benefit from helicopter transportation, but it has been difficult to separate the increased skill of the providers involved from the transport service and the mode of transport.

Trauma center transfers are designed to minimize the time to the appropriate facility. The most common cause of traumatic death is still hemorrhage. Damage control surgery and correction of coagulopathy to optimize hemorrhage control have become the practice paradigm for civilian and military trauma care. Therefore, time to surgery is an important factor and drives the need for rapid transfer to the facility that can perform the appropriate procedure. This applies in the newly forming stroke centers and cardiac centers as well. Cardiac centers have shown a survival benefit from percutaneous coronary intervention (PCI) initiated as close to the cardiac event as possible. However, studies have shown more complications¹⁴ with helicopters or minimal time benefit¹⁵ with helicopters in cardiac patients. Stroke centers also have a benefit from medication or intra-arterial procedures within certain time frames.¹⁶ In certain conditions, mechanical devices like intra-aortic balloon pumps (IABP) and extracorporeal membrane oxygenation (ECMO) are being used earlier in care plans, which has pushed critical care transport teams to be able to move patients while on these complicated devices.

Pediatric transfer systems have been established to provide more generalized critical care than trauma, cardiac, or stroke systems. A recent study suggested that having a more specialized transport team was more important than the time delay in response.¹⁷ The study found a higher rate of unplanned events during transport and mortality with less specialized teams. There has been significant debate over the level of knowledge needed by the transport team. Studies have found no benefit to adding a physician to the pediatric transport team.^{18,19}

In the current era of cost containment, some systems have looked at using transfers to help contain outside-system costs. Kaiser Permanente implemented a plan to transfer patients with chest pain complaints from community emergency departments to one of their facilities.²⁰ They showed no specific deterioration in the care provided but also did not analyze the actual cost of this process.

The concept of regionalization of adult critical care that is being discussed²¹ would require the identification and classification of facilities. Regionalization has the possibility for benefits in standardization and cost control. A definite volume–outcome benefit has not been proved. As transport systems are developed for this new concept, it will be important to consider the type of system to be created. Will it look like the pediatric transfer model, with the receiving

center providing the transport oversight, or like the trauma model, with the sending facility responsible for choosing the transport agency? The EMTALA passed as part of the Consolidated Omnibus Budget Reconciliation Act in 1985 makes the referring provider responsible for ensuring safe and optimal transport.

AIR TRANSPORT CONSIDERATIONS

Boyle's law describes the inverse relationship between pressure and volume in gases. Basically, gas expands as pressure decreases. This can present significant problems when transporting patients by air. As the aircraft increases its altitude, the pressure decreases. This causes problems for gas-filled structures in closed spaces and diffusion across the alveolar–capillary membrane. Pressurizing the cabin can return the pressure to sea level. There is a limit to how much pressurization can be achieved, and so, for certain conditions, a lower flying altitude must be maintained, resulting in longer flight times.

Gas-filled structures in closed spaces can cause significant in-flight complications, but with some simple preparation these complications can be avoided. A small pneumothorax that usually would be managed conservatively will need to have a chest tube placed prior to air transport. Chest tubes need to be vented with a one-way valve or a continuous suction device that can operate in hypobaric pressures. Even the gas in the GI system can cause problems, and a nasogastric or orogastric tube needs to be considered prior to transport. Any tube being held in place by a balloon filled with air (endotracheal, Foley, etc.) needs to be monitored closely or filled with saline instead.

For the majority of patients, a simple volume control ventilator is sufficient for transport. However, finding a ventilator that can perform this function accurately at different barometric pressures is limited. The most commonly used ventilator is the Uni-Vent Eagle Model 754 (Impact Instrumentation, Inc., West Caldwell, New Jersey).²² The ventilator can perform volume control ventilation with up to 20 cm of positive end-expiratory pressure (PEEP) and a maximum inspiratory flow rate of 60 L/min. If the patient requires more significant respiratory management, the transport options are limited to highly specialized teams. The majority of these teams are part of the military.

CREW COMPOSITION AND TRAINING

Crew configuration among critical care transport platforms in the United States is varied not only in composition of licensed personnel, but also in the number of crew members in each team. Some systems utilize two crew members, whereas others have favored utilizing three crew members. When looking at two-member configuration in the United States, the team composition can be made up of EMT/EMT-Critical Care Paramedic, EMT-Paramedic/RN, RN/RT, RN/RN, and RN/MD. The majority of two-crew team composition systems in the United States employ the EMT-Paramedic/RN

configuration.²³ Another challenge related to critical care transport is the lack of national standardization of training and certification across the United States. As the need to transport critically ill/injured patients increases, it is imperative that this capability grow and training be standardized. Review of the rate of reported adverse events during transport of these patients has ranged from 5% to 12%.^{24–26} This finding highlights the importance of focusing on standardized education and training of the crews as well as a robust continuous quality improvement (CQI) program with Medical Director involvement.

MILITARY SYSTEM

Over the years, there have been many advances in military medicine. A significant change involves how critically injured or ill service members are transported to the United States. The movement of critical care patients within the military has evolved to a mature system, capable of transporting very ill or seriously injured patients over long distances in a timely manner. These teams are a fundamental part of the current military medical system that cares for our wounded warriors. Within the US military, there are three primary adult platforms that are used to carry out this mission. The goal of these teams is to conduct seamless ICU-level care while transporting the patient to a higher level of care.

Critical Care Air Transport Teams (CCATT)

The CCATT concept was born in 1994.²⁷ The CCATTs are not a stand-alone platform; they augment the US Air Force Aeromedical Evacuation system, adding a critical-care capability to the system. Their goal is to manage casualties who have undergone initial resuscitation but who remain critically ill while transporting them to a higher level of care.²⁷ A physician leads this team to ensure that the patient has continuous access to medical decision-making. This enables the team to have the inherent capability to titrate therapies and ventilator settings to the patient's condition, start new therapies if required, and perform procedures when needed. The end result is an environment in which patients can continue to progress toward stability without interruption or setback during transport.²⁷

CCATTs are composed of a critical care physician, who may be a general surgeon, pulmonary/critical care physician, anesthesiologist, emergency medicine physician, or a cardiologist. Completing the team are a critical care nurse and a respiratory therapist. CCATTs have the capability of caring for up to three ventilator patients or six less acute patients.^{28,29} This capability can be expanded to five ventilator patients by augmenting the primary CCATT with the addition of a CCATT extender team, which is made up of two critical care nurses.²⁴

CCATTs are experienced and current in the management of critically ill or injured patients with multisystem trauma, open/closed head injuries, shock, burns, respiratory failure,

multiple organ failure, and other life-threatening complications.²⁷ The success of this platform is evident from the operations carried out during Operation Iraqi Freedom and Operation Enduring Freedom.

The acuity of the patients transported by CCATTs is demonstrated by the results of the recent study performed by Laret et al., titled *Short Term Outcomes of US Air Force Critical Care Air Transport Team (CCATT) Patients Evacuated from a Combat Setting*.³⁰ In this study, 656 patient moves were examined retrospectively. The distribution of the transports included 425 (64.8%) patients with traumatic injuries and 231 (35.2%) with medical complaints. When looking at the trauma subset, the mean injury severity score (ISS) was 22 (range 1–75). The breakdown of the type of injury was also impressive, resulting in 269 suffering polytrauma (multisystem) injuries, 80 having amputations, 90 suffering head injuries, 73 suffering burns, 121 having intra-abdominal injuries, and 98 having intrathoracic injuries. The intensity of care during transport reflects the severity of the casualties moved: 318 (48.5%) patient moves required mechanical ventilation, 68 (10.4%) received vasoactive medications, and 43 (6.6%) required blood products administered during the flight.³⁰

The movement of burn casualties has its own inherent challenges due to the severity of the injury, which can include an inhalational component. As with other casualties, the movement includes two phases. In the Middle Eastern conflict region, the first move is from Iraq or Afghanistan to Germany, which is carried out by the Air Force AE system, augmented with CCATT. After arrival in Germany, the next step of transport can be carried out by either CCATT or the US Army Institute of Surgical Research Burn Flight Team (USAISR BFT), according to patient requirements.

US Army Institute of Surgical Research Burn Flight Team

The history of the USAISR BFT is a long one with thousands of burn patients moved to date. The team was formed in 1951 and is based out of Brooke Army Medical Center (BAMC) at Fort Sam Houston, Texas.^{31,32} The team composition includes a general surgeon (team leader) experienced in burn, trauma, and surgical critical care, and two nurses, one of whom serves as the lead flight nurse. This individual is a registered nurse with significant burn and critical care experience. The second nurse of the team is a licensed vocational nurse who has completed the Army's Critical Care Nursing Program. The fourth member of the team is a Certified Respiratory Therapist who has extensive experience in using a variety of ventilators and in treating patients with severe lung disease and inhalational injury. Completing the team is an operations noncommissioned officer who is also a medical technician and both serves as the operations officer for each mission and provides assistance to the flight team as needed.³¹ As with the CCATT, the BFT can be augmented with additional personnel as required by the mission.³¹ A key unique aspect of the BFT over other critical care transport platforms involves continuity of care. The BFT surgeon who assesses

the patient in Germany routinely becomes the attending physician for that patient during the hospitalization in the burn center.³¹

When deciding which platform will transport a burn casualty from Germany to the United States, key factors taken into account are the patient's condition, pulmonary status, and response to conventional ventilatory support.³¹ The BFT personnel are versed in the management of inhalation or pulmonary injury requiring ventilatory support beyond the capabilities of traditional transport ventilators.³¹ If needed, the BFT physician can perform fiberoptic bronchoscopy during the transport of the casualty. In caring for burn casualties during transport, the BFT uses both the volumetric diffusive respirator (VDR-4) and the TXP pressure control ventilator (Percussionaire Corp, Sand Point, Idaho).^{31,33}

After the decision has been made to activate the BFT, the team flies from San Antonio (BAMC) to Germany while the casualty is being transported by CCATT from Iraq or Afghanistan. On arrival, the casualty is evaluated and cared for by the BFT surgeon.

Acute Lung Rescue Team (ALRT)

CCATT has been very effective in moving patients quickly from the conflict theater, at times in just hours after injury and surgical intervention. On occasion, some patients develop severe acute respiratory distress syndrome (ARDS) requiring advanced modes of ventilation. In November 2005, the ALRT was formed to fill this capability of moving these patients from Iraq and Afghanistan to Landstuhl Regional Medical Center (LRMC) in Germany. The ALRT is based at LRMC and is versed in the use of high-frequency percussive ventilation using the VDR-4 (Percussionaire Corp) and other advanced ventilator strategies such as inverse I/E ratio. The team composition includes a trauma or critical care surgeon, a pulmonary or critical care physician, a critical care nurse, and a respiratory therapist who is experienced in the use of the VDR-4 (Percussionaire Corp).³⁴

Between November 2005 and March 2007, the ALRT successfully transported five patients with a mean Pao_2/FiO_2 ratio of 71, consistent with severe ARDS.³⁴ In the same study period, the ALRT was activated for 1% of mechanically ventilated patients brought to LRMC. While CCATT continues to be the primary platform for moving critically injured/ill patients from the conflict theater, having the capability of the ALRT available when needed is fundamental for mission success.

The aircraft used to carry out aeromedical evacuation, including the critical care transport mission, are aircraft of opportunity; their primary mission is not one of medical care. These aircraft have a variety of missions ranging from troop movements to cargo transport. Because of this, all the equipment needed to care for the patient must be brought aboard by the CCATT, USAISR BFT, and ALRT. In effect, the end result is converting the back of an aircraft into a flying ICU. The intertheater missions can be long, extending from 4.5 to 13 hours depending on the destination. Patient

care priorities during transport are the same as those carried out in a trauma ICU regardless of which team carries out the mission. The ultimate goal is to maintain the same standard of care through the continuum of care.

Moving critical care patients has its own inherent challenges created by the environment, such as decreased lighting, vibration, noise, and lack of humidity and temperature regulation, not to mention that the resources available in the back of the aircraft are limited to what the team brings with them. During transport, a primary focus of the team is airway protection and maintenance. Continuous ventilator monitoring is carried out through pulse oximetry and waveform end-tidal CO_2 monitoring. Arterial blood gases are performed to adjust ventilator settings as necessary during the flight. Hemodynamic status is monitored through invasive means (arterial blood pressure and central venous pressure [CVP]). When caring for casualties with a head injury, intracranial pressure (ICP) is monitored with a ventriculostomy or ICP monitor. This information is vital for the team to make appropriate interventions. Blood for transfusions has to be brought on to the aircraft by the team. If needed, the teams have the ability to insert chest tubes and central lines or intubate a patient during transport. The level of care given to these casualties is extraordinary and a testament to advances within military medicine.

TRANSFER CENTERS

The transfer from one facility to another requires many moving parts. We have talked about the transport agencies and options available to move specialized patients. Current market pressures provide that many facilities do not have available capacity. Finding an accepting facility can be difficult and requires significant time on the phone contacting one facility after another. Most hospitals have tried to streamline the process and consolidate the resources needed to accomplish interfacility transfers through a centralized transfer center. In a large academic institution, there can be many different services receiving transfers at the same time. One system even found it more economical to outsource this function due to its complexity.³⁵

In addition to the complexity of finding an appropriate facility, there are significant EMTALA requirements that need to be met. EMTALA has obligations for both the sending and receiving facilities. Sending facilities are required to stabilize the patient to the maximum of his or her capability prior to transferring. In addition, the sending facility is responsible for sending a copy of the patient's complete medical record, including images, and choosing the most appropriate means of transportation including qualified personnel. The receiving facility has an obligation to accept patients from other facilities if they have space available and qualified personnel who can provide the needed service. It is also required that the patient provides a written request to be transferred or a statement from the transferring physician that the medical benefits of transfer outweigh the risks involved.³⁶ A memorandum of transfer helps record all the different pieces

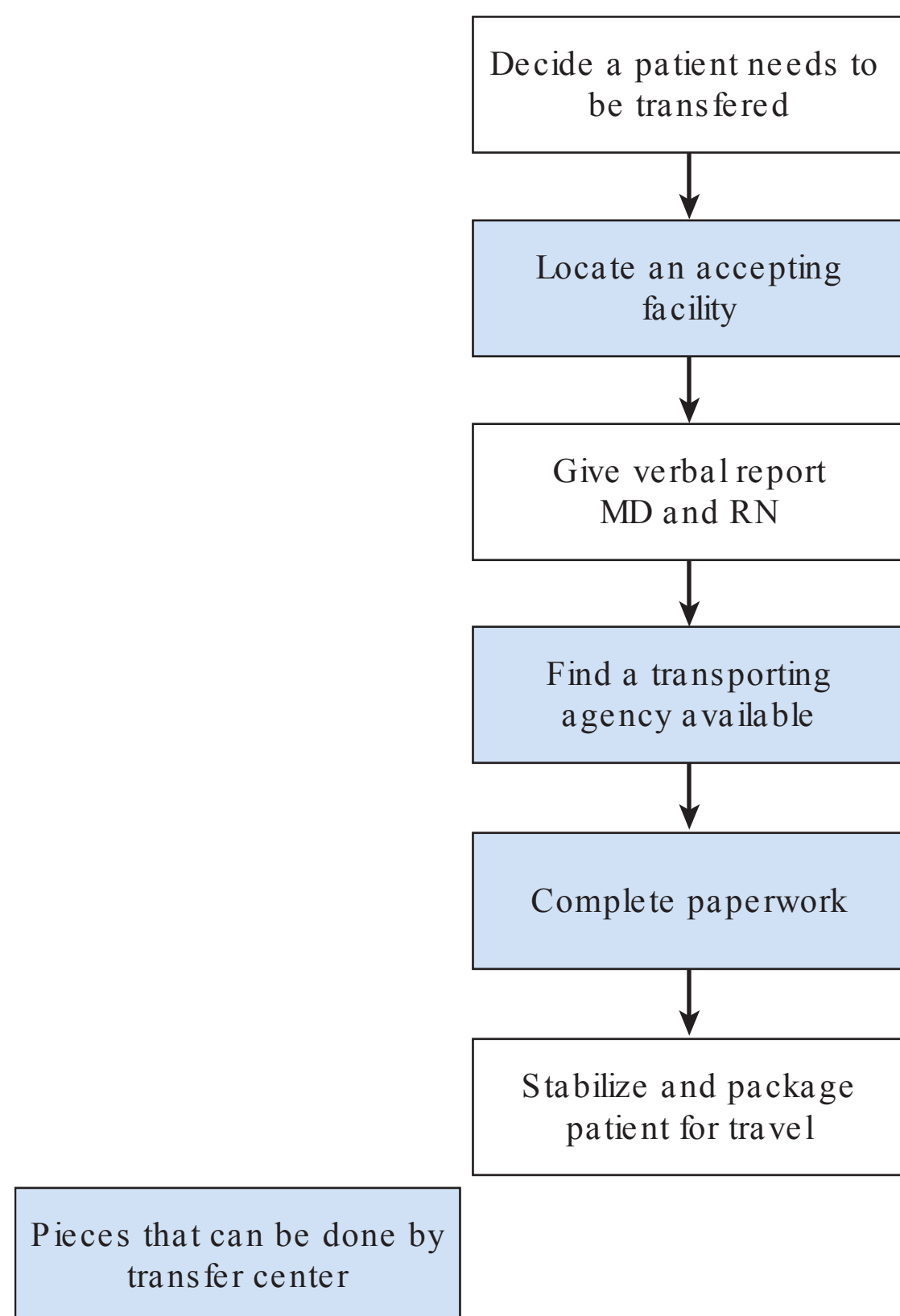


FIGURE 63-2 Transfer flow diagram.

required for a transfer. Having all these pieces organized and streamlined through a central transfer center will speed up the transfer. Figure 63-2 shows a simplified transfer flow pattern and identifies the pieces that a transfer center could be assigned to accomplish.

SUMMARY

Critical care transport decisions are difficult and require significant thought prior to initiating. Therefore, the creation of systems that are designed to take into account these complex issues are important prior to transferring patients. There are many different options of equipment and provider skill levels available in specific teams. As a health care provider on the receiving or sending side of patient transfers, it is important to understand the teams and resources available in your region. As the volume of transfers increases, primary and backup options must be considered when creating transfer pathways.

As financial and specialization considerations make regionalization more likely in the future, it will be important to have a knowledge of critical care transport pitfalls and successes. A strong quality improvement program will help guide the formation of these systems. There is limited research on the true benefits and risks of creating systems of consolidated specialized care. However, there is no doubt that critical care transportation will be an increasing area of focus in the coming decades.

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End-of-Life Issues in Emergency Critical Care

Sangeeta Lamba

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INTRODUCTION

The majority of patients who are admitted to medical and surgical intensive care units (ICUs) often begin their hospital course in the emergency department (ED). Thus, ED clinicians set the stage for the future management trajectory, usually initiating aggressive life-saving measures, with a curative and resuscitative approach to care.^{1,2} Due to advances in technology, deaths in most critically ill patients now often result from limitation of life-supporting measures as opposed to a natural decline from disease or age.³ Since the majority of critically ill patients spend the last few days of their life in a hospital, this has resulted in an expansion of the mission of critical care to include provision of the best care available for dying patients and their families.⁴ In 2003, an International Consensus Conference was convened to discuss some of these end-of-life challenges and to address the issues related to optimal care for dying critical care patients.⁵ In order to achieve the best quality of life desired by the patient rather than just an emphasis on the quantity of life regardless of disease or symptom burden, it has become clear that we need to focus on patient values, beliefs, and comfort from the onset of care, regardless of their diagnosis.^{2,4,5}

Essential to the goal of providing good end-of-life care is understanding a few key concepts: (1) death is not a professional failure, (2) a pain-free death must be assured, (3) effective communication with family and surrogates is needed for shared decision-making, (4) goals-of-care discussions help guide the “shift” from a curative to a comfort approach,

and, most importantly, (5) a multidisciplinary team to support patient and family needs throughout the dying process is absolutely essential. This multidisciplinary team ideally would include nurses, physicians in training, social workers, family support personnel, chaplains, and, when appropriate and available, subspecialist palliative care consult teams.⁶ We further discuss the following domains frequently encountered in end-of-life care provision: (1) advance directives; (2) goals-of-care discussions and communication; (3) death-related issues that include delivery of bad news, death notification, and family-witnessed resuscitation (FWR); (4) withdrawal of life support; and (5) palliative care with optimal symptom management at end of life.

ADVANCE DIRECTIVES

Management of a patient at end-of-life is expected to be based on an understanding of what the patient wants and values, shared decision-making, and a respect for patient autonomy. Currently, decision-making in critical care patients varies widely and may not always allow for shared decision-making and may not always defer to patient autonomy.^{5,7,8} For example, one major study reported that physicians did not consistently document a do not resuscitate (DNR) order for patients who did not wish to have cardiopulmonary resuscitation (CPR),⁷ whereas another showed that even when DNR orders were present, these were followed only 58% of the time.⁸ Discussions about care plans made jointly with patient

and family necessitate either a patient who is able to express his or her desires or a designated person/family that is able to do same on behalf of the patient no longer able to communicate. This involves determining the decision-making capacity of patient and often offering assistance to surrogate decision-makers as discussed later.

Determining Decision-Making Capacity

Determining if a patient has the ability and capacity to make a health care-related decision is an essential step toward assessing patient needs and values. The decision-making capacity is often considered in the context of the specific medical decision that needs to be made and is therefore *decision-specific*.⁹ This means that the patient may have the capacity to make one particular decision (often straightforward and simple) but not have the same capacity for another decision (often more complex). Physicians are responsible for judging *capacity* related to the specific medical care decisions, whereas *competency* to manage one's life matters is assessed by a judge. A list of questions to help assess capacity include: (1) Can the patient understand and process the information? This requires him or her to relay back the content to you in lay terms. (2) Can the patient analyze and understand consequences? This essentially means he or she is able to weigh the risks or benefits and to communicate the reasoning behind his or her decision. (3) Can the patient communicate his or her choice? This is particularly difficult in the nonverbal, ventilator-dependent patient who may not be able to convey the elements essential to an informed consent or decision. His or her attempts may be prone to a biased interpretation based on the values of the person obtaining consent.⁹ A patient for whom the answer to any of these questions is "no" essentially lacks decision-making capacity. The clinician then has to consider and engage those who are the surrogate decision-makers on behalf of the patient.

Surrogate Decision-Making for Patients Unable to Make Medical Decisions

Advance directives or surrogate decision-makers come into play only when a person lacks decision-making capacity. Living wills or written advance directives are rarely found to be at hand in emergent situations and, even if available, are often not specific enough to be applied to all routine, day-to-day medical decisions.¹⁰ The main value of such documents is perhaps in the event of imminent death when a specific choice of no mechanical ventilation or no cardiopulmonary resuscitation (CPR) is requested. In critical and emergent situations, the availability and access to a patient's designated legally authorized representative, surrogate, proxy, or durable power of attorney for health care decisions is more helpful and important for day-to-day decision-making. Using a surrogate, though, has its own limitations; some studies have found that surrogates may often fail to accurately represent the patient's wishes,¹¹ whereas others have shown that family members have high rates of anxiety and depression that may compromise their ability to make effective decisions on the patient's

behalf.¹² It is important for clinicians to guide the surrogates early in order to make sure they understand their role in making decisions for the patient. Many have summarized that the role of a surrogate is to provide a "substituted judgment" for the incapacitated patient based on his or her knowledge of the patient and previous statements made by the patient, and the decisions should not be based primarily on the surrogate's own values.^{11,12} In the event of no available pre-identified, legally authorized surrogate, family members are often involved in decision-making. In many states, a hierarchy of decision-making responsibility may be as follows: spouse, adult child, parent, adult sibling, adult relative, and then a close friend. In cases of interfamily conflict, involvement of ethics committees or court guidance may sometimes become necessary. Despite a surrogate, major decisions will often also involve the approval of most close family members, and effective communication therefore becomes an essential tool for the clinician.¹³

GOALS-OF-CARE DISCUSSIONS AND EFFECTIVE COMMUNICATION

In surveys of critical care patients' families, it is reported that families consistently rate communication as among their most important concerns and often report dissatisfaction with the manner in which they were informed about the

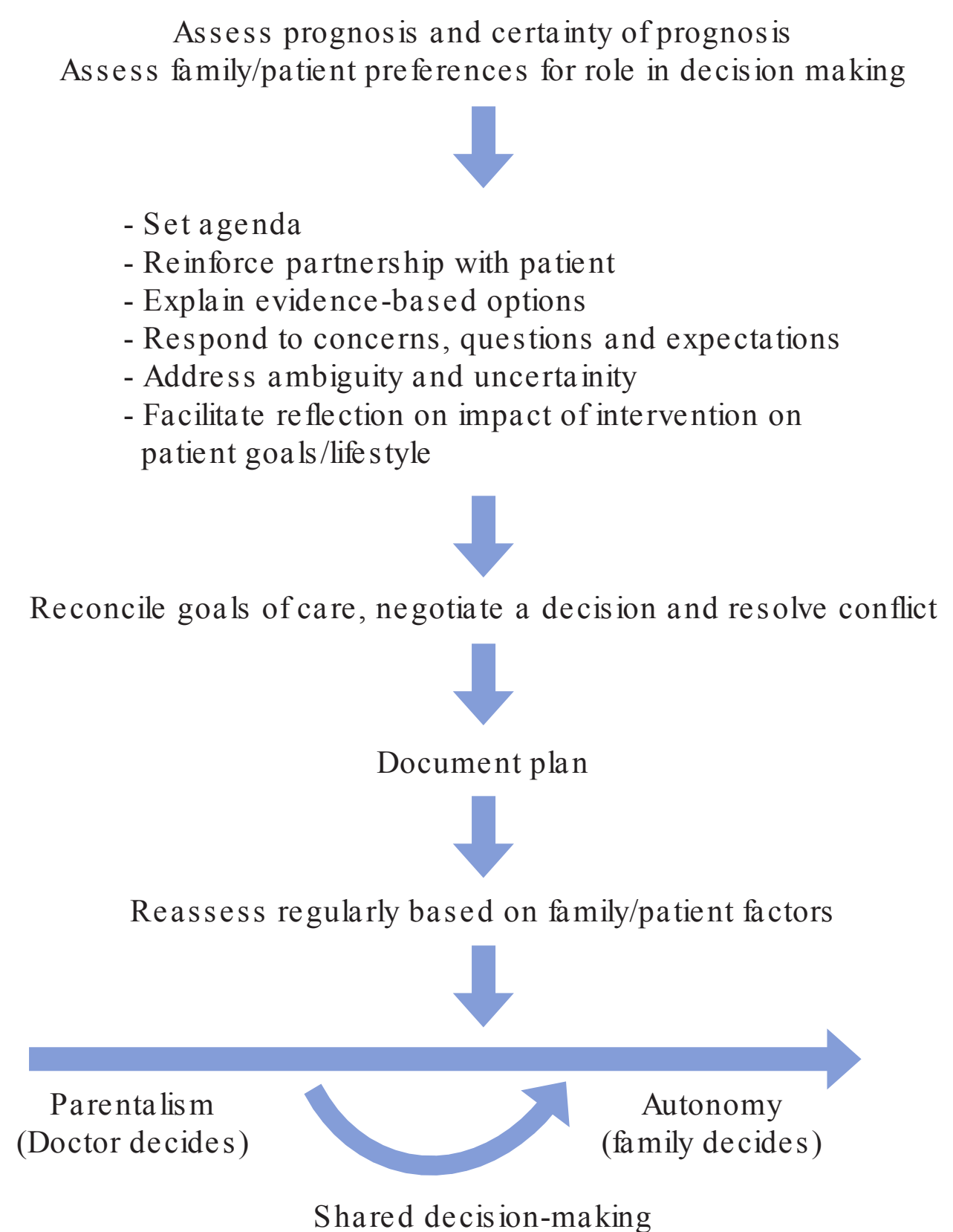


FIGURE 64-1 Multistep approach to patient- and family-centered decision making that is modified by prognosis and by family preferences. Modified with permission from Curtis JR, White DB: Practical guidance for evidence-based ICU family conferences, *Chest*. 2008 Oct;134(4):835–843.

diagnosis, prognosis, and treatment and in general the quality of communication with the critical care staff.^{7,10,14,15} Models of communication are being increasingly addressed in critical care literature and emphasize a shared decision-making, proactive approach to resolving conflicts and reaching consensus (Figure 64-1).^{5,13,16–19} Guidelines suggest that when conducting family conferences, clinicians should consider the specific needs of families that have been previously identified in studies, such as reassurance that the patient's symptoms will be managed; clear information conveyed to caregivers about the patient's condition and treatment; a willingness of staff to listen and respond to family members and to address their emotions; a valuing of patient preferences; clear explanations about surrogate decision-making; and reassurance of continuous, compassionate, and technically proficient care until death occurs.¹⁷ Decisions should generally be made collaboratively by clinicians partnering with patients' families. Treatment choices should be crafted to meet specific,

achievable goals.²⁰ The process is one of negotiation, and the outcome will finally be determined by the personalities and beliefs of the participants. Ultimately, it is the physician's responsibility to decide on how reasonable a planned action may be. If a conflict cannot be easily resolved, an ethics consultation may be helpful.^{4,5} Communication with family members is not different from other aspects of critical care and requires training, interdisciplinary teamwork, and implementation of effective and flexible protocols to achieve the best possible outcome (Table 64-1).^{13,18,21}

CARE AROUND DEATH AND DYING

Delivery of Difficult News Related to Poor Prognosis or Death

Delivery of difficult news, especially death notification, is perhaps the most difficult, emotionally laden communication



TABLE 64-1: Family Conference Process Steps

1. **Why are you meeting:** Clarify conference goals of what you hope to accomplish.
2. **Where:** A room with comfort, privacy, and circular seating.
3. **Who:** Patient (if capable); legal decision maker/health care power of attorney; family members; social support; key health care professionals.
4. **Introduction and relationship building**
 - Introduce self/others; review meeting goals and which decisions need to be made.
 - Establish ground rules: each person will have a chance to ask questions and express views; no interruptions; identify legal decision maker; and describe importance of supportive decision making.
 - If you are new to the patient/family, spend time seeking to know the “person”—ask about hobbies, family, what is important in his or her life, etc.
5. **Determine what the patient/family already knows.** Tell me your understanding of the current medical condition? Ask everyone in the room to speak. Also ask about the past 1–6 months—what has changed in terms of functional decline, weight loss, etc.
6. **Review medical status**
 - Review current status, prognosis, and treatment options.
 - Ask each family member in turn if they have any questions about current status, plan, and prognosis.
 - Defer discussion of decision making until the next step.
 - Respond to emotional reactions (see Fast Facts #29, 59, 224).
7. **Family discussion with a decisional patient**
 - Ask the patient: What decision(s) are you considering?
 - Ask each family member: Do you have questions or concerns about the treatment plan? How can you support the patient?
8. **Family discussion with a non-decisional patient**
 - Ask each family member in turn: What do you believe the patient would choose if the patient could speak for him- or herself?
 - Ask each family member: What do you think should be done?
 - Ask if the family would like you to leave room to let family discuss alone.
 - If there is consensus, go to 10; if no consensus, go to 9.
9. **When there is no consensus:**
 - Re-state: What would the patient say if they could speak? Ask: Have you ever discussed with the patient what he or she would want in a situation like this?
 - If you, as a clinician, have a firm opinion about the best plan of care, recommend it simply and explicitly, and explain why.
 - Use time as ally: schedule a follow-up conference the next day.
 - Try further discussion: What values is your decision based upon? How will the decision affect you and other family members?
 - Identify other resources: Minister/priest; other physicians; ethics committee.
10. **Wrap-up:**
 - Summarize consensus, disagreements, decisions, and plan.
 - Caution against unexpected outcomes.
 - Identify family spokesperson for ongoing communication.
 - Document in the chart who was present, what decisions were made, follow-up plan.
 - Don't turf discontinuation of treatment to nursing.
 - Continuity—Maintain contact with family and medical team. Schedule follow-up meetings as needed.

task that physicians perform.^{22,23} Physicians often report factual medical information but avoid the most stressful issues and have trouble with empathic disclosures.²³ Stressors include the physician's fear of being blamed, the difficulty in dealing with surviving family members' emotions, and the physician's own personal fear of death.²⁴ ED death notifications may be especially difficult for physicians because (1) ED deaths are often sudden and/or unexpected, due to an acute traumatic event, or may involve young previously healthy patients; (2) there is usually no pre-existing relationship between the physician and the patient or family; (3) the chaotic, public environment of the ED itself may not be suitable for the family to grieve privately; and (4) clergy or social service support staff may not be readily available, especially during off hours.^{22,25} Various methods to inform families of the death of a loved one exist, and it is important to remember that the clinician has a responsibility toward the survivors since the words spoken to them will linger in their memories and influence the grieving process.^{22,23,26} The GRIEV_ING mnemonic has been shown to improve physician confidence and competence in death notification in emergency medicine. This method is outlined in Table 64-2. It may be important for each clinician to refine the particular language he or she uses in such situations, rehearse a stepwise approach to decrease his or her own stress, and review the terminology in advance when using a translator. With the rapid growth of telecommunications, it is best that phones and beepers be switched to a vibrate mode so there are no interruptions when delivering difficult news to family. It is also recommended



TABLE 64-2: Guidelines for the Approach to Families in Death Notification

The GRIEV_ING mnemonic for death notification

G—gather; ensure that all family members are present

R—resources; private location, call for support resources available to assist the family with their grief, that is, chaplain, bereavement counselors, and friends

I—identify; identify yourself, identify the deceased or injured patient by name, and identify the level/state of knowledge of the family relative to the events and patient condition

E—educate; educate briefly as to the events that have occurred and the current status in the emergency department

V—verify; verify that their family member has died. Be clear! Use the D-words “dead” or “died”

—space; give the family personal space and time for emotions; allow time to absorb the news

I—inquire; ask if there are any questions, and answer to the best of ability

N—nuts and bolts; inquire about organ donation, funeral services, and personal belongings. Offer the family the opportunity to view the body

G—give; give them access information. Offer to answer questions that may arise later and return their calls

that clinicians sit down to emphasize the importance of being available for questions and not rush through the delivery, in addition to considering bringing in an interdisciplinary team to support the family (social work, chaplain, nursing). Delivering the news appropriately with compassion will ease the grief period and allows loved ones to reclaim their lives.²⁶

Family-Witnessed Resuscitation

Recent literature advocates family member presence during CPR.^{27–30} The perceived benefits of family-witnessed resuscitation (FWR) are the following: (1) most family members prefer to be given the option to be with the patient at time of death; (2) although such experiences are emotionally draining, they may assist in bereavement and decrease complicated grief; (3) FWR may reduce overall fear or anxiety, (4) provide a higher sense of connection with the patient, (5) remove doubt that everything possible was done for the loved one, and finally (6) provide a feeling of closure.^{27–30} Provider attitudes, though, continue to represent a barrier to FWR. These include concerns that family involvement might cause distress for survivors, interfere in the resuscitation, distract or intimidate the team, bring greater pressure to prolong the code, cause anxiety in pronouncing death, and may lead to increased malpractice litigation when, in fact, family members are probably less likely to seek medical litigation if they feel everything possible was done.^{29,30} There also appears to be more hesitation in the urban setting as compared with suburban, possibly due to lack of adequate ancillary support or the underlying nature of the types of resuscitations.³⁰ The concerns cited with FWR include the issues of (1) human dignity, (2) personal privacy, and (3) the provision of adequately trained staff to help relatives cope with the emotional trauma that the experience of being a witness may invoke. FWR should be performed with an assigned individual (usually a designated nurse) whose role is to be present with, support, and explain the resuscitation to the family member. However, most would agree that a multidisciplinary, well-planned, and practiced approach is necessary for FWR and should be used to develop and enhance an institutional protocol, to address staff concerns, and to train family facilitators.³⁰

WITHDRAWAL OF NONBENEFICIAL INTERVENTIONS

When analyzed closely, it is clear that almost all patients who die while receiving critical care do so as a result of either withholding or withdrawing of life-sustaining interventions.³ Sometimes, the decision is made to withhold and not resuscitate the patient prior to the terminal decompensation and at other times because even multiple, vigorous resuscitation attempts have failed to halt the terminal decline and cannot be provided indefinitely.³ The practice of withholding or withdrawal of life-sustaining interventions varies among countries and institutions.^{31,32} Withdrawal of nonbeneficial life support measures is sometimes necessary early in the care of a critical patient in the ED: for example, if a patient

was initially placed on mechanical ventilation and the family wishes withdrawal of the ventilator based on patient's previously expressed wishes or based on acceptance of the extremely poor prognosis in the case of a catastrophic intracranial bleed.

Ethically, there exists no distinction between the decisions to withdraw a specific treatment or intervention and a decision not to initiate an intervention.³¹ Sometimes, however, initiating a "time-limited trial" of aggressive therapy may actually be beneficial to family and caregivers and necessary in order for them to come to terms with a critical patient's condition; this trial may allow clinicians to adequately evaluate all available treatment options.³¹ As with any other treatment, if this trial does not improve status and fails to show any benefit to the patient, then there exists justification for its withdrawal. CPR is the therapy most often withheld, and DNR orders may precede up to 60% of all deaths.^{3,7,33} Mechanical ventilation, vasoactive drugs, renal dialysis, and antibiotics are the other therapies commonly withheld. Not surprisingly, the most commonly withdrawn therapy prior to patient death is mechanical ventilation, followed by vasoactive drugs.^{3,33–35}

Many algorithms exist for medical management of withdrawal of ventilator support in the ED.^{36–39} The decision to withdraw or withhold a life-prolonging intervention such as a ventilator if there exists no benefit to the patient is best achieved by a consensus between the critical care team and family. Discussions with surrogates should be frank and consistent. Withholding or withdrawal of specific life support interventions should be recommended, not merely listed as an option. The rationale used to come to this recommendation, including prognostication and disease-specific data, should be communicated to family in clear terms without medical jargon.^{13,19,21} Often, to reach consensus, multiple meetings may be necessary after the initial recommendation.³³ It is also advisable not to make CPR the focus of discussions, but rather to focus on the goals of care, which should help define whether a therapy will be withheld or withdrawn.

Once the decision is made to withdraw mechanical ventilation and nonbeneficial treatments, all interventions usually should be stopped including vasopressors, mechanical ventilation, and antibiotics.^{36,38,39} Family and caregivers should be made aware that death may not happen instantaneously, and, in fact, some patients may survive for many hours post ventilator withdrawal.³³ In all cases, a humane, pain-free process should be assured and the family presence at bedside encouraged. The administration of sedatives and analgesics must not hasten death; in one study, median time to death following the withholding/withdrawal of life-sustaining measures was 3.5 hours in patients who received such drugs compared with 1.3 hours in those who did not.³⁷ Both extubation and gradual weaning have been used, and, regardless of approach used, patients should be pre-medicated and have staff present at bedside to answer concerns during and after the process.^{38,39} One such protocol suggests the following steps: (1) first, discontinue all paralytics, allowing full return of neuromuscular function; (2) disable all alarms; (3)

titrate sedation to comfort—continuous infusions are least obtrusive; (4) reduce FiO₂ to room air and PEEP to zero over ≤ 5 minutes; (5) gradually reduce volume and pressure support over 20–30 minutes; and, finally, (6) once the patient is comfortably sedated on these settings, extubate or change to a T-piece.

Disagreements can occur among family members and also between caregivers and clinicians around withdrawal or withholding of treatments, especially when some may strongly believe in preserving life at all costs because of cultural or religious beliefs. Such disagreements can cause tension and moral distress among both families and clinicians. Again, a multidisciplinary approach with a dedicated staff who has received prior training might facilitate and ease such end-of-life decision-making, and support for family should be provided.

PALLIATIVE CARE AND OPTIMAL SYMPTOM MANAGEMENT

The Ethics Committee of the Society of Critical Care Medicine in 2001 and the consensus conference in 2003 published guidelines based on identified end-of-life needs of patients, families, and providers.^{4,5,31} Previously identified *patients'* needs at end of life are to receive adequate pain management, avoid inappropriate prolongation of dying, achieve a sense of control, relieve themselves of burdens, and strengthen their relationships with loved ones.^{7,40,41} The *families'* identified needs are to be with their loved one during the dying process, be helpful to their loved one, be kept informed of the changing clinical status, understand the process of what and why therapy is being done, be assured of the patients' comfort, be comforted themselves, express their own emotions, be assured that their decisions regarding the patients were correct, and find meaning in the dying of their loved ones.^{5,17} The identified needs of the *health care providers* are to establish consensus regarding the goals, have strategies for providing palliative care, gain knowledge and skills in palliation, be supported in their tasks by their institutions, and have opportunities for grieving and bereavement after their patients' death.^{5,31}

Close attention to the principles of good pain management, communication with patient and family, and discussion of goals of care are not just for patients who are at the end-of-life, but are appropriate care for all critically ill patients, regardless of prognosis. In this framework, "intensive care" encompasses palliative and curative care.^{2,42} With the recent growth in the palliative care field, many hospitals may have subspecialist-level, expert, formal consultation teams to assist the critical-care and ED physicians in many of the end-of-life issues discussed earlier.^{1,2} However, most institutions still lack such palliative team support, and a multidisciplinary approach to care with involvement of nursing, social workers, bereavement, and family support teams may help maximize utilization of institutional resources.

Optimal symptom management at end of life should remain the focus of the clinician, whether a curative or a comfort approach to patient care is being followed.^{4,5,42,43}

Management of uncontrolled pain and avoidance of oligoanalgesia based on prior misconceptions is necessary. Cautious individual titration of opioids to analgesic effect is safe, effective, and rarely associated with addiction, clinically significant respiratory depression, rapid tolerance, or euphoria.^{42,44} The use of pain assessment tools especially in the nonverbal patients, frequent reassessments, and therapy that is geared toward objective and subjective endpoints may facilitate this goal.

The patient must be provided with sufficient analgesia to alleviate pain and distress; if such analgesia hastens death, this “double effect” should not detract from the primary aim to ensure comfort.^{5,31} The concept of double effect has been invoked to guide decision-making in many end-of-life situations, for example, in *terminal or palliative sedation*, the practice of using sedatives in the terminally ill at doses that render a patient unconscious as a last resort measure to provide relief from suffering due to distressing symptoms of dyspnea or pain.^{45–47} This practice is to be clearly differentiated from euthanasia or physician-assisted suicide, in which the intent is to cause death. Recently, the Supreme Court has unanimously ruled that there is no constitutional right to physician-assisted suicide. However, it went with a majority, effectively requiring all states to ensure that their laws do not obstruct the provision of adequate palliative care, especially for the alleviation of pain and other physical symptoms of people facing death.⁴⁷ One Supreme Court Justice even stated, “a patient who is suffering from a terminal illness and who is experiencing great pain has no legal barrier to obtaining medication, from qualified physicians, to alleviate that suffering, even to the point of causing unconsciousness.” Unlike euthanasia, most terminal sedation protocols require titration at fixed intervals to reassess underlying symptoms and ongoing need, with the intent to provide optimal symptom relief at the *lowest* therapy dose. As always, frank and detailed conversations with family and caregivers are necessary prior to any major therapeutic interventions.^{45–47}

RESOURCES

The integration and practice of emergency palliative and end-of-life care shares many similarities with integration of palliative care into intensive care units.^{48,49} The critical-care integrative approach has a rich peer-reviewed literature defining techniques, and outcomes of integrative strategies and now the literature for emergency palliative care is increasing.^{48–55} Multiple tools and resources are described in the literature to improve care for patients at end of life.^{48–50} Some of these include “Fast Facts and Concepts” that provide concise, practical, peer-reviewed, and evidence-based summaries on key topics important to clinicians caring for dying patients, such as how to hold a goals-of-care conversation or how to care for the patient under hospice care.^{18,48–50,56} Another resource is the integrating palliative care into the intensive care unit (IPAL-ICU) and integrating palliative care into emergency medicine (IPAL-EM) projects from the Center to Advance Palliative Care.^{48,49,57} These offer an online portal

for best evidence, tools, and practical resources to assist clinicians. The website is continually updated, and new peer-reviewed tools representing best practices are being developed with the aid of an oversight board of nationally recognized interdisciplinary leaders in the field of critical care, EM, and palliative care.^{48,49,57}

CONCLUSION

For provision of optimal end-of-life care to critical patients, it is recommended that clinicians (1) refer to and be guided by the basic ethical principles of patient autonomy, beneficence, and nonmaleficence; (2) recognize the necessity to shift from a curative to comfort care approach and consider the limitations of life-prolonging, nonbeneficial interventions when the clinical situation is clearly hopeless; (3) base the decision-making process to ascertain hopelessness of a clinical situation on a thorough patient evaluation and an ample time course; (4) communicate effectively with family/surrogates for shared decision-making; (5) document discussions and decisions; (6) use a multidisciplinary approach to end-of-life care; and, finally, (7) implement thorough palliative care and symptom management strategies once the decision to withhold or withdraw life-sustaining interventions has been made.⁵

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